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WO 02/14311 A2

(54) Title: UREA COMPOUNDS AND METHODS OF USES

(57) Abstract: Selected novel urea compounds are effective for prophylaxis and treatment of diseases, such as cell proliferation or apoptosis mediated diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving stroke, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

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**UREA COMPOUNDS AND METHODS OF USES**

This application claims the benefit of U.S. Provisional Application No. 60/225,793, filed August 15, 2000, which is hereby incorporated by reference.

**5 FIELD OF THE INVENTION**

This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating cell proliferation-related disorders and apoptosis-related disorders.

**BACKGROUND OF THE INVENTION**

Identification of therapeutic agents effective in the treatment of neoplastic diseases or for the treatment of neurological disorders is the subject of significant research efforts.

Protein kinases represent a large family of proteins which play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. A partial list of such kinases includes abl, ATK, bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, TRK, Yes, and Zap70. As such, inhibition of kinases has become an important therapeutic target.

Cell proliferation is the rapid reproduction of cells, such as by cell division. The cell cycle, which controls cell proliferation, is itself

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controlled by a family of kinases called cyclin dependent kinases (CDKs). The regulation of CDK activation is complex, and requires the association of the CDK with a member of the cyclin family of regulatory subunits. A further level of regulation occurs through both activating and inactivating phosphorylations of the CDK subunit. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Both the critical G1-S and G2-M transitions are controlled by the activation of different cyclin/CDK activities. Loss of control of CDK regulation is a frequent event in hyperproliferative diseases and cancer. (T. Noguchi et al., Am. J. Pathol., 156, 2135-47 (2000)) As such, inhibition of CDKs has become an important target in the study of chemotherapeutics (A. Senderowicz and E. Sausville, J. Nat. Canc. Instit., 92, 376-87 (2000))

Kinases have also been implicated in diseases and disorders of the central nervous system. For example, patients suffering from stroke, Alzheimer's disease or Parkinson's disease would benefit from the inhibition of kinases. Cdk5 has been shown to be involved in Alzheimer's pathology (R. Maccioni, et al., Eur. J. Biochem., 268, 1518-27 (2001)) and with neuronal development (G. Paglini and A. Caceres, Eur. J. Biochem., 268, 1528-33 (2001)).

Protein kinases also control programmed cell death, also known as apoptosis. Apoptosis is a ubiquitous physiological process used to eliminate damaged or unwanted cells in multicellular organisms.

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Disregulation of apoptosis is believed to be involved in the pathogenesis of many human diseases. The failure of apoptotic cell death has been implicated in various cancers, as well as autoimmune disorders.

- 5 Conversely, increased apoptosis is associated with a variety of diseases involving cell loss such as neurodegenerative disorders and AIDS. As such, inhibition of apoptosis has become an important therapeutic target. Cdk5 has been shown to be involved
- 10 in apoptosis pathology (A. Catania et al., Neuro-Oncology, 89-98 (April 2001)).

- Substituted heterocyclic compounds are known in the pesticide art. WO00/24735, published 4 May 2000, describes 1-pyridyl-1,2,4-triazoles as pesticides.
- 15 WO00/24739, published 4 May 2000, describes substituted 1,2,4-triazoles as pesticides. WO97/01552, published 16 January 1997, describes substituted 1,2,4-triazoles as antifungal agents. DE4204492 describes substituted benzamides as pesticides. WO98/57969, published 23
- 20 December 1998, describes heterocyclylpyridines as pesticides. GB2293380, published 27 March 1996, describes the use of heterocyclic compounds as pesticides. United States patent No. 5,693,667, issued Dec. 2, 1997, describes heterocyclic compounds for the
- 25 treatment of take-all disease. EP468695 describes fungicide compounds. United States patent No. 5,294,596, issued March 15, 1994, describes herbicidal triazolinones. United States patent No. 5,395,818, issued March 7, 1995, describes herbicidal
- 30 triazolinones.

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Substituted thiazoles also are known in the pesticide art. United States patent No. 4,260,765, issued Apr. 7, 1981, describes 2-(3-pyridyl)-5-thiazolecarboxamides for the treatment of aphids.

- 5 United States patent No. 5,945,380, issued Aug. 31, 1999, describes 4-(4-pyridyl)pyrazoles as insecticides. WO89/00568, published 26 January 1989, describes nicotine derivatives as fungicides.

- Heterocyclic ureas are known in the pharmaceutical art. WO99/23091, published 14 May 1999, describes heterocyclic compounds as anti-inflammatories. WO99/32455, published 1 July 1999, describes heterocyclic ureas as RAF kinase inhibitors. WO99/32110, published 1 July 1999, describes heterocyclic ureas as p38 kinase inhibitors. WO99/32106, published 1 July 1999, describes heterocyclic ureas as RAF kinase inhibitors. WO99/32111, published 1 July 1999, describes heterocyclic ureas as p38 kinase inhibitors. WO99/32436, published 1 July 1999, describes urea compounds as inhibitors of RAF kinase. WO99/32463, published 1 July 1999, describes urea compounds that inhibit p38 kinase. WO98/52558, published 26 November 1998, describes urea compounds for the inhibition of p38 kinase. WO99/00357, published 7 January 1999, describes the use of urea compounds as inhibitors of p38 kinase. WO99/58502, published 18 November 1999, describes urea compounds as inhibitors of p38 kinase. US patent 5,821,245, issued Oct. 13, 1998, describes substituted naphthalene derivatives for treating cell growth. GB patent 1,437,895 describes 2-thiazolyl

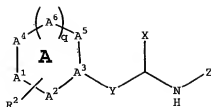
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- ureas for the treatment of ulcers. United States patent 5,364,871, issued Nov. 15, 1994 describes thiazoles as anti-ulcer compounds. WO99/21555, published 6 May 1999, describes pyridyl-substituted thiazoles as adenosine A3 receptor antagonists. WO96/23783 describes indole derivatives as 5-HT receptor antagonists. United States patent No. 5,208,248 describes indazole derivatives as 5-HT receptor antagonists. WO99/46244, published 16 September 1999 describes heterocyclic compounds as tyrosine phosphatases. GB patent 2,263,109, published 14 July 1993, describes pyridylthiazoles as PAF-receptor antagonists.
- Thiazole compounds have also been described as inhibitors of CDK. WO00/26203, published 11 May 2000, describes 2-ureidothiazoles as inhibitors of cdk. WO99/65884 describes 2-aminothiazoles as inhibitors of CDK. WO99/24416 describes 2-aminothiazoles as inhibitors of CDK.
- However, compounds of the current invention have not been described as inhibitors of cell proliferation or apoptosis such as for the treatment of cancer or stroke.

## 25 DESCRIPTION OF THE INVENTION

A class of compounds useful in treating cell proliferative disorders, neurological disorders and apoptosis is defined by Formula I

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I

wherein each of A<sup>1</sup>-A<sup>6</sup> is selected from CH<sub>2</sub>, CH, C, O, S, NH and N; wherein A<sup>1</sup>-A<sup>6</sup> together form a ring A  
 5 selected from

- a) additionally substituted or unsubstituted 5- or 6-membered heterocyclyl, preferably 5- or 6-membered heteroaryl, more preferably 5-membered heteroaryl selected  
 10 from thiazolyl, oxazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl, and 6-membered heteroaryl selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl,  
 15 even more preferably 5-membered heteroaryl selected from thiazolyl, oxazolyl and imidazolyl, and 6-membered heteroaryl selected from pyridyl, and pyrimidinyl,

- 20 b) additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group,

- c) additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, preferably 5-membered cycloalkenyl, more preferably cyclopentadienyl or cyclopentenyl, and  
 25 d) additionally substituted or unsubstituted phenyl,

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wherein A is additionally substituted with one or more substituents independently selected from halo,  $-OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-NR^3C(O)R^3$ , cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted phenyl, lower alkyl, cyano, lower hydroxyalkyl, nitro, lower alkenyl, lower alkynyl and lower haloalkyl, preferably one or more substituents independently selected from halo,  $-OR^3$ ,  $-SR^3$ ,  $-S(O)R^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-NR^3C(O)R^3$ ,  $C_1-C_2$  alkyl, cyano,  $C_1-C_2$  hydroxyalkyl, nitro,  $C_2-C_3$  alkenyl,  $C_2-C_3$  alkynyl and  $C_1-C_2$  haloalkyl, more preferably one or more substituents independently selected from fluoro, hydroxy, methoxy, amino and methyl;

wherein X and Z taken together form a nitrogen containing ring selected from unsubstituted 5-6 membered heterocyclyl, unsubstituted 5-6 membered heterocyclyl fused with a phenyl group, 5-6 membered heterocyclyl substituted with one or more substituents independently selected from  $R^1$ , and 5-6 membered nitrogen-containing heterocyclyl, fused with a phenyl group, substituted with one or more substituents independently selected from  $R^1$ ,

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preferably a ring selected from substituted or unsubstituted 5- or 6-membered nitrogen-containing heteroaryl, and substituted or unsubstituted 5- or 6-membered nitrogen-containing heteroaryl fused with a phenyl group,

5 more preferably substituted or unsubstituted thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, isoindolyl, indolyl, indazolyl, purinyl, [1,6]naphthyridinyl, 5,6,7,8-tetrahydro[1,6]naphthyridinyl, isoquinolyl and quinolyl,

10 even more preferably pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, [1,6]naphthyridinyl and 5,6,7,8-tetrahydro[1,6]naphthyridinyl,

15 most preferably pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl,

most preferred pyridyl;

wherein  $R^1$  is independently selected from H, halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -CONR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>,

20 cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted 4-10 membered heterocyclylalkyl, optionally substituted phenyl,

25 optionally substituted phenoxy, lower alkyl, lower cyano, lower alkenyl, lower alkynyl and lower haloalkyl,

preferably optionally substituted pyrrolidinyl, optionally substituted piperazinyl, optionally substituted piperidinyl, morpholinyl, optionally substituted pyridyl, 1,4-dioxo-8-aza-

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spiro[4.5]decyl, optionally substituted phenyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkyl, amino, C<sub>1</sub>-C<sub>4</sub>-azidoalkyl, C<sub>1</sub>-C<sub>4</sub>-cyanoalkyl, C<sub>1</sub>-C<sub>4</sub>-aminoalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl (optionally substituted pyrrolidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperazinyl)-C<sub>1</sub>-C<sub>2</sub>-, 4-morpholinyl-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted imidazolyl)-C<sub>1</sub>-C<sub>2</sub>-, phthalimidylethyl, optionally substituted azepanyl-C<sub>1</sub>-C<sub>2</sub>-, 1,4-dioxa-8-aza-spiro[4.5]decyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted pyridyloxy, optionally substituted phenoxy, tetrahydrofuryl-O-, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted phenoxy-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 5-6-membered N-containing heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, aminocarbonyl, C<sub>1</sub>-C<sub>3</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino and C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino,

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more preferably 3-(N,N-dimethylamino)-1-pyrrolidinyl, 1-methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, 5 piperidinyl, morpholinyl, 4-amino-1-piperidinyl, 4-(N-hydroxyethylamino)-1-piperidinyl, 4-(N-propylamino)-1-piperidinyl, 4-(N-benzylamino)-1-piperidinyl, 4-oxo-piperidinyl, 4-(hydroxyimino)-piperidinyl, 4-morpholinyl, 1,4-dioxo-8-aza-10 spiro[4.5]decyl, pyridyl, phenyl, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, amino, azidomethyl, hydroxymethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, fluoro, chloro, bromo, aminoethyl, aminomethyl, 15 cyanomethyl, 1-pyrrolidinyl-CH<sub>2</sub>-, 2-methoxycarbonyl-1-pyrrolidinyl-CH<sub>2</sub>-, 2-carboxy-1-pyrrolidinyl-CH<sub>2</sub>-, 2-hydroxymethyl-1-pyrrolidinyl-CH<sub>2</sub>-, 1-piperidinyl-CH<sub>2</sub>-, 4-methyl-1-piperidinyl-CH<sub>2</sub>-, 3-methyl-1-piperidinyl-CH<sub>2</sub>-, 2-methyl-1-20 piperidinyl-CH<sub>2</sub>-, 3,5-dimethyl-1-piperidinyl-CH<sub>2</sub>-, 4-oxo-1-piperidinyl-CH<sub>2</sub>-, 4-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 3-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 2-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-carboxy-1-25 piperidinyl-CH<sub>2</sub>-, 4-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-propylamino)-1-piperidinyl-CH<sub>2</sub>-, 1-methyl-4-30 piperazinyl-CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, (2-methyl-1-imidazolyl)-CH<sub>2</sub>-, 3-(N,N-diethylamino)carbonyl-1-

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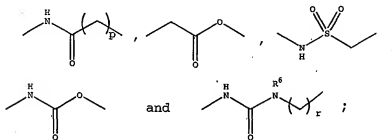
piperidinyl-CH<sub>2</sub>-, phthalimidylethylenyl, 1-azepanyl-CH<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-CH<sub>2</sub>-, 4-(methyl)phenoxymethylenyl, 4-(N,N-dimethylaminomethylenyl)phenoxymethylenyl, 5 methylaminothiocarbonyl, methoxymethylenyl, ethylaminothiocarbonyl, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminoethylenyl, N-methylaminomethylenyl, N-10 (hydroxypropyl)aminomethylenyl, N-ethylaminomethylenyl, Boc-aminoethoxymethylenyl, aminoethoxymethylenyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, 2-pyrrolidinylmethoxy, 1-methyl-2-pyrrolidinylmethoxy, azetidin-3-ylmethoxy, N-Boc-15 azetidin-3-ylmethoxy, N-Boc-piperidin-4-ylethoxy, 1-methyl-4-piperidinylethoxy, 4-piperidinylmethoxy, N,N-dimethylaminoethoxy, 3-tetrahydrofuryl-O-, 3-tetrahydrofurylmethoxy, 4-tetrahydrofurylmethoxy, 4-methylphenoxy, 4-20 (aminoethyl)phenoxy, 4-(1-imidazolyl)phenoxy, 2,4-dimethylphenoxy, phenoxy, 4-cyanophenoxy, 4-[1,3]dioxolan-2-ylphenoxy, 4-fluorophenoxy, 3,4-difluorophenoxy, ethoxycarbonyl, morpholinylethylenylaminocarbonyl, 25 morpholinylpropylenylaminocarbonyl, 1-piperidinylcarbonyl, methylaminocarbonyl, ethylaminocarbonyl, N,N-diethylaminocarbonyl, N-(N',N'-dimethylaminoethylenyl)aminocarbonyl, aminocarbonyl, morpholinylethylenylamino, 30 morpholinylpropylenylamino, N,N-diethylamino, N,N-dimethylamino, N,N-diethylamino(2-

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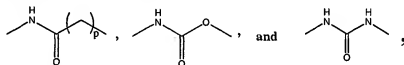
propylenyl)aminomethylenyl, N,N-diethylamino(1-propylenyl)aminomethylenyl and N-(N',N'-dimethylaminoethylenyl)amino;

wherein Y is selected from

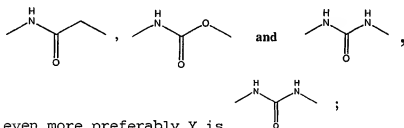
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preferably Y is selected from



10 more preferably Y is selected from



even more preferably Y is

15 wherein R<sup>2</sup> is selected from

- a) lower alkylaminoalkynyl,
- b) cycloalkenyl-C<sub>2-3</sub>-alkynyl,
- c) cycloalkyl-C<sub>2-3</sub>-alkynyl,
- d) phenyl-C<sub>2-3</sub>-alkynyl,
- 20 e) 5-6 membered heterocyclyl-C<sub>2-3</sub>-alkynyl,
- f) substituted or unsubstituted cycloalkenyl,

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- g) substituted or unsubstituted phenyl,  
h) substituted or unsubstituted 5-6 membered heterocyclyl, and  
i) substituted or unsubstituted 5-6 membered heterocyclyl bridged with a phenyl group,  
5 preferably substituted phenyl, substituted or unsubstituted 5-6 membered nitrogen-containing heteroaryl, and substituted or unsubstituted 5-6 membered nitrogen-containing heteroaryl fused with a phenyl group,  
10 more preferably substituted or unsubstituted substituted phenyl or a substituted or unsubstituted heterocyclyl substituent selected from thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl and quinolyl,  
15 even more preferably phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, purinyl, isoquinolyl and quinolyl,  
20 most preferably pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, preferred pyridyl;
- wherein substituted  $R^2$  is substituted with one or more substituents independently selected from halo,  $-OR^3$ ,  
25  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-NR^3R^3$ ,  $-C(O)NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-NHC(O)R^3$ ,  $-SO_2NHC(O)R^3$ ,  $-C(S)NR^3R^3$ , nitro, cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 4-7 membered heterocyclyl, optionally substituted  
30 heterocyclylalkylenyl, optionally substituted phenyl, optionally substituted phenoxyalkylenyl,

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optionally substituted heterocyclyloxyalkyl, lower alkyl, cyano, lower hydroxyalkyl, lower alkoxyalkyl, lower azidoalkyl, lower aminoalkyl, lower (hydroxyalkyl)aminoalkyl, lower alkylaminoalkyl, lower alkylaminoalkoxy, lower aminoalkoxyalkyl, lower (alkylaminoalkyl)amino lower ((alkylamino)alkylamino)alkyl, lower alkylaminoalkylaminocarbonyl, lower cyanoalkyl, lower alkenyl, lower alkynyl and lower haloalkyl, preferably selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, halo, amino, C<sub>1</sub>-C<sub>2</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkoxy-C<sub>1</sub>-C<sub>2</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>2</sub>-alkylthio, cyano, C<sub>1</sub>-C<sub>2</sub>-haloalkyloxy, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylaminocarbonyl, nitro, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylaminosulfonyl, C<sub>1</sub>-C<sub>2</sub>-alkylaminosulfonyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkylaminosulfonyl, phenyl-C<sub>1</sub>-C<sub>2</sub>-alkylaminosulfonyl, (optionally substituted phenyl)aminosulfonyl, piperidinyl, morpholinyl, C<sub>1</sub>-C<sub>2</sub> alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub> alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, aminocarbonyl, C<sub>1</sub>-C<sub>2</sub>-alkylcarbonylamino, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino, C<sub>1</sub>-C<sub>2</sub>-alkylamino and C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino, more preferably selected from nitro, methylcarbonylamino, aminosulfonyl, phenylsulfonylamino, morpholinylsulfonyl, trifluoroacetylaminosulfonyl, (4-chlorophenyl)aminosulfonyl, hydroxy,

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methylthio, cyano, trifluoromethoxy, bromo, chloro, fluoro, amino, methoxy, ethoxy, ethoxymethyl, trifluoromethylcarbonylamino, trifluoroethoxy, pyridyl, phenyl, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, carboxy, methylthio, piperidinyl, morpholinyl, N-methylpiperazinyl, N-ethylpiperazinyl, methylaminothiocarbonyl, N-methylamino-methylenyl, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N,N-dimethylamino, N-methylaminoethylenyl, N,N-diethylamino, morpholinylethylenylaminocarbonyl, morpholinylpropylenylaminocarbonyl, aminocarbonyl, morpholinylethylenylamino, morpholinylpropylenylamino, N,N-dimethylamino and N,N-di-methylaminoethylenylamino;

wherein R<sup>3</sup> is selected from H, lower alkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocyclcyl, optionally substituted heterocyclcylalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and lower haloalkyl, preferably H, C<sub>1</sub>-C<sub>3</sub> alkyl, phenyl, 5-6 membered heteroaryl, C<sub>5</sub>-C<sub>8</sub> cycloalkyl, and C<sub>1</sub>-C<sub>3</sub> haloalkyl; more preferably H, methyl, ethyl, optionally substituted phenyl, benzyl, and trifluoromethyl;

wherein R<sup>6</sup> is selected from H, alkyl, 5-6 membered heterocyclcylalkylenyl and alkylamino, preferably H;

wherein p is 1-2, preferably p is 1;

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wherein q is 0 or 1; and

wherein r is 0, 1, 2 or 3, preferably 0 or 1, more preferably 0;

and pharmaceutically acceptable salts thereof;

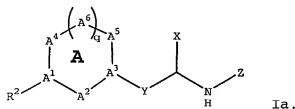
5 provided A is not thiazol-2-yl when Y is ureido;

further provided A is not phenyl when R<sup>2</sup> is pyridyl or pyrimidyl when Y is ureido and when X and Z taken together form 1-methylindolyl; further provided A is not 1-phenylpyrazol-4-yl when Y is ureido when X and

10 Z taken together form pyrazolyl and when R<sup>2</sup> is pyrrol-1-yl; further provided A is not thiazolyl or dihydrothiazolyl when R<sup>2</sup> is indolyl when Y is ureido and when X and Z taken together form thiazolyl or dihydrothiazolyl; provided A is not thiazolyl when  
15 R<sup>2</sup> is 3-pyridyl when Y is ureido and when X and Z taken together form 2-(3-pyridyl)thiazol-4-yl; and further provided A is not thien-3-yl when Y is ureido when X and Z taken together form thienyl and when R<sup>2</sup> is pyrrol-1-yl.

20

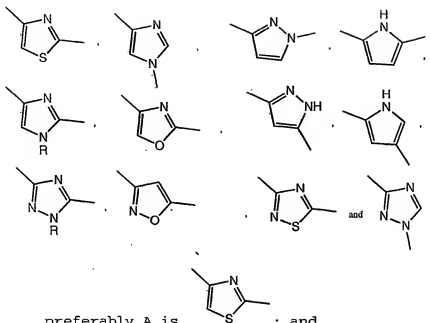
The invention also relates to compounds of Formula Ia




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The invention also relates to compounds of Formula I wherein A is selected from

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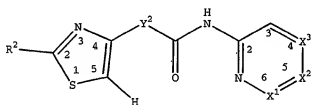
preferably A is  ; and

wherein R is selected from H and C<sub>1</sub>-C<sub>3</sub> alkyl; and pharmaceutically acceptable salts thereof.

5

The invention also relates to compounds of Formula

II



II

10

wherein X<sup>1</sup> is CR<sup>1</sup> or N; wherein X<sup>2</sup> is CR<sup>1</sup> or N; wherein X<sup>3</sup> is CH or N; provided only one of X<sup>1</sup>, X<sup>2</sup> and X<sup>3</sup> can be N;

wherein R<sup>1</sup> is one or more substituents selected from H,  
 15 optionally substituted pyrrolidinyl, optionally substituted piperazinyl, optionally substituted

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piperidinyl, morpholinyl, 1,4-dioxo-8-aza-spiro[4.5]decyl, pyridyl, phenyl, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkyl, amino, C<sub>1</sub>-C<sub>4</sub>-azidoalkyl, C<sub>1</sub>-C<sub>4</sub>-cyanoalkyl, C<sub>1</sub>-C<sub>4</sub>-aminoalkyl, halo, hydroxy, (optionally substituted pyrrolidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperazinyl)-C<sub>1</sub>-C<sub>2</sub>-, morpholinyl-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted imidazolyl)-C<sub>1</sub>-C<sub>2</sub>-, phthalimidyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted azepanyl-C<sub>1</sub>-C<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted phenoxy-C<sub>1</sub>-C<sub>2</sub>-, C<sub>1</sub>-C<sub>4</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted azetidyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-O-, tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted pyridyloxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, aminocarbonyl, 5-6-membered N-containing heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino;

wherein R<sup>2</sup> is selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>2</sub>-C<sub>4</sub>-alkynyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl,

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optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, unsubstituted 5-membered oxygen or sulfur containing heteroaryl, unsubstituted 6-membered nitrogen-containing heterocyclyl, phenyl optionally substituted with one or two substituents selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkylamino, amino, nitro, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonylamino, (optionally substituted phenyl)sulfonylamino, cyano, C<sub>1</sub>-C<sub>2</sub>-haloalkoxy, 5- or 6-membered N-containing heterocyclyl, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylaminosulfonyl and (optionally substituted phenyl)aminosulfonyl, and 6-membered nitrogen-containing heterocyclyl substituted with one or more substituents independently selected from pyridyl, phenyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy, amino, halo, piperidinyl, morpholinyl, C<sub>1</sub>-C<sub>2</sub> alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub> alkylaminothiocarbonyl, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, N-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, aminocarbonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylamino, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino and N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino; and

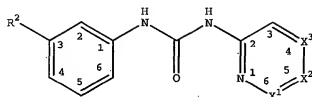
wherein Y<sup>2</sup> is selected from O, NH and CH<sub>2</sub>;

and pharmaceutically acceptable salts thereof.

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The invention also relates to compounds of Formula

III



III

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wherein  $X^1$  is  $CR^1$  or N; wherein  $X^2$  is  $CR^1$  or N; wherein  $X^3$  is CH or N; provided only one of  $X^1$ ,  $X^2$  and  $X^3$  can be N;

preferably  $X^1$  is  $CR^1$ ;  $X^2$  is  $CR^1$ ;  $X^3$  is CH; provided  $X^2$

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is CH when  $X^1$  is not CH;

wherein  $R^1$  is one or more substituents independently selected from H, optionally substituted

pyrrolidinyl, optionally substituted piperazinyl, optionally substituted piperidinyl, morpholinyl,

15

1,4-dioxo-8-aza-spiro[4.5]decyl, pyridyl, phenyl,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_2$ -haloalkyl,  $C_1$ - $C_4$ -hydroxyalkyl, amino,  $C_1$ - $C_4$ -azidoalkyl,  $C_1$ - $C_4$ -cyanoalkyl,  $C_1$ - $C_4$ -aminoalkyl, halo, hydroxy, (optionally substituted pyrrolidinyl)- $C_1$ - $C_2$ -, (optionally substituted

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piperidinyl)- $C_1$ - $C_2$ -, (optionally substituted piperazinyl)- $C_1$ - $C_2$ -, morpholinyl- $C_1$ - $C_2$ -, (optionally substituted imidazolyl)- $C_1$ - $C_2$ -, phthalimidyl- $C_1$ - $C_2$ -, optionally substituted azepanyl- $C_1$ - $C_2$ -, 1,4-dioxo-8-aza-spiro[4.5]decyl- $C_1$ - $C_2$ -, optionally substituted

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phenoxy- $C_1$ - $C_2$ -,  $C_1$ - $C_4$ -alkylaminothiocarbonyl,  $C_1$ - $C_4$ -alkoxy- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -hydroxyalkylamino- $C_1$ - $C_4$ -alkyl, amino- $C_1$ - $C_4$ -alkoxy- $C_1$ - $C_4$ -alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy,

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optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy,  
optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy,  
optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-O-,  
5 tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted  
pyridyloxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-  
alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-  
alkylaminocarbonyl, 5-6-membered N-containing  
heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-  
10 C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl,  
aminocarbonyl, 5-6-membered N-containing  
heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-C<sub>4</sub>-  
alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino,  
15 preferably H, methyl, ethyl, propyl, 1-methyl-4-  
piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-  
pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-  
piperazinyl, 1-ethyl-4-piperazinyl, 1-piperidinyl-  
CH<sub>2</sub>-, 4-methyl-1-piperidinyl-CH<sub>2</sub>-, 3-methyl-1-  
20 piperidinyl-CH<sub>2</sub>-, 2-methyl-1-piperidinyl-CH<sub>2</sub>-,  
3,5-dimethyl-1-piperidinyl-CH<sub>2</sub>-, 4-oxo-1-  
piperidinyl-CH<sub>2</sub>-, 4-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 3-  
hydroxy-1-piperidinyl-CH<sub>2</sub>-, 2-ethoxycarbonyl-1-  
piperidinyl-CH<sub>2</sub>-, 3-ethoxycarbonyl-1-piperidinyl-  
25 CH<sub>2</sub>-, 3-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-  
ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-carboxy-1-  
piperidinyl-CH<sub>2</sub>-, 4-(1-pyrrolidinyl)-1-  
piperidinyl-CH<sub>2</sub>-, 4-(N-hydroxyethylamino)-1-  
piperidinyl-CH<sub>2</sub>-, 4-(N-propylamino)-1-piperidinyl-  
30 CH<sub>2</sub>-, 3-(N,N-diethylamino) carbonyl-1-piperidinyl-  
CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, N,N-

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dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminomethylenyl, N-ethylaminomethylenyl and N,N-diethylamino, more preferably ethyl, propyl, 1-methyl-4-

5 piperazinyl, 1-piperidinyl-CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, N,N-diethylaminomethylenyl and N,N-diethylamino; and

wherein R<sup>2</sup> is selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>2</sub>-C<sub>4</sub>-alkynyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl,

10 optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, unsubstituted 5-membered oxygen or sulfur containing heteroaryl, unsubstituted 5- or 6-membered nitrogen-containing heterocyclyl, phenyl

15 optionally substituted with one or two substituents selected

from halo, C<sub>1</sub>-C<sub>4</sub>-alkylamino, amino, nitro, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonylamino, (optionally

20 substituted phenyl)sulfonylamino, cyano, C<sub>1</sub>-C<sub>2</sub>-haloalkoxy, 5- or 6-membered N-containing heterocyclyl, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylamino-sulfonyl and (optionally

25 substituted phenyl)aminosulfonyl, and

6-membered nitrogen-containing heterocyclyl substituted with one or more substituents independently selected from pyridyl, phenyl,

C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy, amino,

30 halo, piperidinyl, morpholinyl, C<sub>1</sub>-C<sub>2</sub> alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub> alkylaminothiocarbonyl,

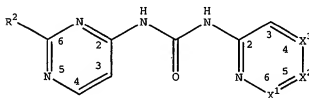
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N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, N-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, aminocarbonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylamino, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino and N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino, preferably 3-(N,N-dimethylamino)-1-propynyl, 3-fluorophenyl, 4-fluorophenyl, 4-(N,N-dimethylamino)phenyl, 3-(methylcarbonylamino)phenyl, phenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminophenyl, 3-aminophenyl, 4-aminosulfonylphenyl, 4-(4-morpholinylsulfonyl)phenyl, 4-(trifluoroacetylaminosulfonyl)phenyl, 4-(trifluoromethylcarbonylaminosulfonyl)phenyl, 4-[(4-chlorophenyl)aminosulfonyl]phenyl, 3-(phenylsulfonylamino)phenyl, 2,4-difluorophenyl, 2,4-dimethoxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 4-methylthiophenyl, 4-cyanophenyl, 4-trifluoromethoxyphenyl, 4-methoxyphenyl, 3-nitrophenyl, 3-methoxyphenyl, 2-methoxyphenyl, 2-thiazolyl, 2-pyrazinyl, 5-pyrimidinyl, 4-methyl-1-piperazinyl, 4-morpholinyl, 6-methoxy-3-pyridyl, 2-methoxy-3-pyridyl, 2-ethoxy-3-pyridyl, 3,4-dichloro-4-pyridyl, 6-(trifluoromethylcarbonylamino)-3-pyridyl, 6-amino-3-pyridyl, 3,5-dichloro-4-pyridyl, 2-chloro-4-pyridyl, 3-pyridyl and 4-pyridyl,

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more preferably 5-pyrimidinyl, 2-pyrazinyl,  
 morpholinyl, 4-methylpiperazinyl, 4-  
 fluorophenyl, 4-(N,N-dimethylamino)propynyl, 3-  
 nitrophenyl, 3-aminophenyl, 4-  
 5 aminosulfonylphenyl, 3-aminosulfonylphenyl, 3-  
 (phenylsulfonylamino)phenyl, 3-  
 (methylcarbonylamino)phenyl, 4-  
 [(trifluoromethylcarbonyl)aminosulfonyl]phenyl,  
 4-hydroxyphenyl, 4-methoxyphenyl, 2-thiazolyl,  
 10 6-(trifluoromethylcarbonylamino)-3-pyridyl, 6-  
 amino-3-pyridyl, 3-pyridyl and 4-pyridyl;  
 and pharmaceutically acceptable salts thereof.

The invention also relates to compounds of Formula  
 15 IV



IV

wherein  $X^1$  is  $CR^1$  or N; wherein  $X^2$  is  $CR^1$  or N; wherein  
 20  $X^3$  is CH or N; provided only one of  $X^1$ ,  $X^2$  and  $X^3$  can  
 be N;  
 preferably  $X^1$  is  $CR^1$ ;  $X^2$  is  $CR^1$ ;  $X^3$  is CH; provided  $X^2$   
 is CH when  $X^1$  is not CH;  
 wherein  $R^1$  is one or more substituents selected from H,  
 25 optionally substituted pyrrolidinyl, optionally  
 substituted piperazinyl, optionally substituted  
 piperidinyl, morpholinyl, 1,4-dioxo-8-aza-  
 spiro[4.5]decyl, pyridyl, phenyl,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_2$ -

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haloalkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkyl, amino, C<sub>1</sub>-C<sub>4</sub>-  
azidoalkyl, C<sub>1</sub>-C<sub>4</sub>-cyanoalkyl, C<sub>1</sub>-C<sub>4</sub>-aminoalkyl, halo,  
hydroxy, (optionally substituted pyrrolidinyl)-C<sub>1</sub>-C<sub>2</sub>-  
, (optionally substituted piperidinyl)-C<sub>1</sub>-C<sub>2</sub>-,  
5 (optionally substituted piperazinyl)-C<sub>1</sub>-C<sub>2</sub>-,  
morpholinyl-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted  
imidazolyl)-C<sub>1</sub>-C<sub>2</sub>-, phthalimidyl-C<sub>1</sub>-C<sub>2</sub>-, optionally  
substituted azepanyl-C<sub>1</sub>-C<sub>2</sub>-, 1,4-dioxo-8-aza-  
spiro[4.5]decyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted  
10 phenoxy-C<sub>1</sub>-C<sub>2</sub>-, C<sub>1</sub>-C<sub>4</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>4</sub>-  
alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-  
C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy-  
C<sub>1</sub>-C<sub>4</sub>-alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy,  
optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy,  
15 optionally substituted azetidyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy,  
optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-O-,  
tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted  
pyridyloxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-  
20 alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-  
alkylaminocarbonyl, 5-6-membered N-containing  
heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl,  
aminocarbonyl, 5-6-membered N-containing  
25 heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-C<sub>4</sub>-  
alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino,  
preferably methyl, ethyl, propyl, 1-methyl-4-  
piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-  
30 pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-  
piperazinyl, 1-ethyl-4-piperazinyl, 1-

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- piperidinyl-CH<sub>2</sub>-, 4-methyl-1-piperidinyl-CH<sub>2</sub>-, 3-methyl-1-piperidinyl-CH<sub>2</sub>-, 2-methyl-1-piperidinyl-CH<sub>2</sub>-, 3,5-dimethyl-1-piperidinyl-CH<sub>2</sub>-, 4-oxo-1-piperidinyl-CH<sub>2</sub>-, 4-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 3-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 2-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-propylamino)-1-piperidinyl-CH<sub>2</sub>-, 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminomethylenyl, N-ethylaminomethylenyl and N,N-diethylamino, and more preferably ethyl, propyl and 1-methyl-4-piperazinyl; and
- wherein R<sup>2</sup> is halo, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>2</sub>-C<sub>4</sub>-alkynyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, 5-membered oxygen or sulfur containing heteroaryl, 5- or 6-membered nitrogen-containing heterocyclyl, phenyl optionally substituted with one or two substituents selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkylamino, amino, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, cyano, C<sub>1</sub>-C<sub>2</sub>-haloalkyloxy, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-

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haloalkylcarbonylaminosulfonyl, and (optionally substituted phenyl)aminosulfonyl, and 6-membered nitrogen-containing heterocyclyl substituted with one or more substituents

- 5 independently selected from pyridyl, phenyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy, halo, piperidinyl, morpholinyl, C<sub>1</sub>-C<sub>2</sub> alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub> alkylaminothiocarbonyl, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, N-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, aminocarbonyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino and N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino,
- 10 preferably 3-fluorophenyl, 4-fluorophenyl, 4-(N,N-dimethylamino)phenyl, 3-(methylcarbonylamino)phenyl, phenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminophenyl, 3-aminophenyl, 4-aminosulfonylphenyl, 4-(4-morpholinylsulfonyl)phenyl, 4-(trifluoroacetylaminosulfonyl)phenyl, 4-(trifluoromethylcarbonylaminosulfonyl)phenyl, 4-[(4-chlorophenyl)aminosulfonyl]phenyl, 3-(phenylsulfonylamino)phenyl, 2,4-difluorophenyl, 2,4-dimethoxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 4-methylthiophenyl, 4-cyanophenyl, 4-trifluoromethoxyphenyl, 4-methoxyphenyl, 3-nitrophenyl, 3-methoxyphenyl, 2-methoxyphenyl, 2-thiazolyl, 2-pyrazinyl, 5-
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- 25
- 30

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pyrimidinyl, 4-methyl-1-piperazinyl, 4-morpholinyl, 6-methoxy-3-pyridyl, 2-methoxy-3-pyridyl, 2-ethoxy-3-pyridyl, 3,4-dichloro-4-pyridyl, 6-(trifluoromethylcarbonylamino)-3-pyridyl, 6-amino-3-pyridyl, 3,5-dichloro-4-pyridyl, 2-chloro-4-pyridyl, 3-pyridyl and 4-pyridyl, and

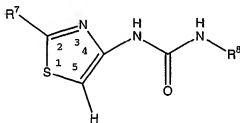
more preferably 4-pyridyl;

and pharmaceutically acceptable salts thereof.

10

The invention also relates to compounds of Formula

V



V

wherein R<sup>7</sup> is selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, 5-membered oxygen or sulfur containing heteroaryl, 6-membered nitrogen-containing heterocyclyl, phenyl optionally substituted with one or two substituents selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkylamino, amino, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, cyano, C<sub>1</sub>-C<sub>2</sub>-haloalkyloxy, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylaminosulfonyl, and (optionally substituted phenyl)aminosulfonyl, and

25

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6-membered nitrogen-containing heterocyclyl  
substituted with one or more substituents

independently selected from pyridyl, phenyl, C<sub>1</sub>-  
C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy, halo,  
5 piperidinyl, morpholinyl, C<sub>1</sub>-C<sub>2</sub> alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub> alkylaminothiocarbonyl, N,N-di-C<sub>1</sub>-C<sub>2</sub>-  
alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, N-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-  
C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-

alkylenylaminocarbonyl, aminocarbonyl,

10 morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino, N,N-di-C<sub>1</sub>-C<sub>2</sub>-  
alkylamino and N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-  
alkylenylamino,

preferably halo, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl,

optionally substituted pyrimidinyl,

15 morpholinyl, optionally substituted

piperidinyl, optionally substituted

benzodioxolyl, optionally substituted indolyl,

optionally substituted phenoxy, optionally

substituted thienyl, phenyl optionally

20 substituted with one or two substituents

selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkylamino, Boc-

amino, amino, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-haloalkyl,

hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, cyano, C<sub>1</sub>-C<sub>2</sub>-

haloalkyloxy, aminosulfonyl, (6-membered N-

25 containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-

haloalkylcarbonylaminosulfonyl, and

(optionally substituted phenyl)aminosulfonyl,

and pyridyl optionally substituted with one or two

substituents selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>4</sub>-

30 alkoxy and halo,

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more preferably bromo, chloro, fluoro, C<sub>1</sub>-C<sub>3</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, optionally substituted pyrimidinyl, morpholinyl, piperidinyl, benzodioxolyl, indolyl, phenoxy, thienyl, phenyl optionally substituted with one or two substituents selected from fluoro, N,N-dimethylamino, amino, methoxy, trifluoromethyl, Boc-amino, hydroxy, ethoxy, methylthio, cyano, trifluoromethoxy, aminosulfonyl, 4-morpholinylsulfonyl, trifluoroacetylaminosulfonyl, and (4-chlorophenyl)aminosulfonyl, and pyridyl optionally substituted with one or two substituents selected from C<sub>1</sub>-C<sub>3</sub> alkyl, methoxy, ethoxy and chloro, even more preferably bromo, methyl, ethyl, cyclopropyl, cyclohexyl, 3-fluorophenyl, 4-fluorophenyl, 4-(N,N-dimethylamino)phenyl, phenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminophenyl, 3-aminophenyl, 4-Boc-aminophenyl, 4-aminosulfonylphenyl, 4-(4-morpholinylsulfonyl)phenyl, 4-(trifluoroacetylaminosulfonyl)phenyl, [(4-chlorophenyl)aminosulfonyl]phenyl, 2,4-difluorophenyl, 5-benzodioxolyl, 2,4-dimethoxyphenyl, 3-hydroxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 4-methylthiophenyl, 5-indolyl, 4-

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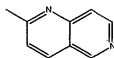
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cyanophenyl, 4-trifluoromethoxyphenyl, 4-methoxyphenyl, 3-methoxyphenyl, 2-methoxyphenyl, phenoxy, 2-thienyl, 4-pyrimidinyl, 2-methylthio-4-pyrimidinyl, morpholinyl, 4-piperidinyl, 6-methoxy-3-pyridyl, 2-methoxy-3-pyridyl, 2-ethoxy-3-pyridyl, 3,4-dichloro-4-pyridyl, 3,5-dichloro-4-pyridyl, 2-chloro-4-pyridyl, 3-pyridyl and 4-pyridyl; and

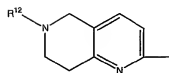
10 wherein R<sup>8</sup> is selected from



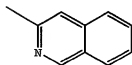
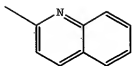
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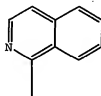
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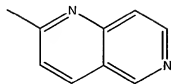
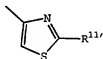
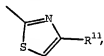
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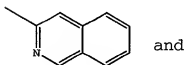
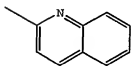
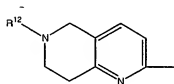
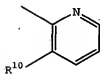
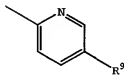
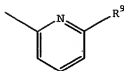
and



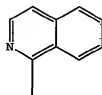
preferably



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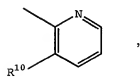
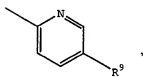
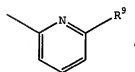
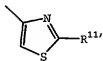
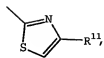


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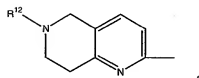
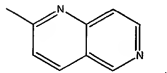


5 more preferably

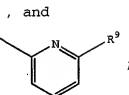
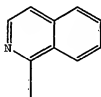
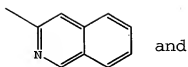
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even more preferably

wherein  $R^8$  is optionally substituted with one or two

substituents independently selected from H,

optionally substituted pyrrolidinyl, optionally

substituted piperazinyl, optionally substituted

piperidinyl, morpholinyl, 1,4-dioxo-8-aza-

spiro[4.5]decyl, pyridyl, phenyl,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_2$ -haloalkyl,  $C_1$ - $C_4$ -hydroxyalkyl, amino,  $C_1$ - $C_4$ -azidoalkyl,  $C_1$ - $C_4$ -cyanoalkyl,  $C_1$ - $C_4$ -aminoalkyl,

halo, hydroxy, (optionally substituted

pyrrolidinyl)- $C_1$ - $C_2$ -, (optionally substitutedpiperidinyl)- $C_1$ - $C_2$ -, (optionally substitutedpiperazinyl)- $C_1$ - $C_2$ -, morpholinyl- $C_1$ - $C_2$ -, (optionallysubstituted imidazolyl)- $C_1$ - $C_2$ -, phthalimidyl- $C_1$ - $C_2$ -,optionally substituted azepanyl- $C_1$ - $C_2$ -, 1,4-dioxo-8-aza-spiro[4.5]decyl- $C_1$ - $C_2$ -, optionally substitutedphenoxy- $C_1$ - $C_2$ -,  $C_1$ - $C_4$ -alkylaminothiocarbonyl,  $C_1$ - $C_4$ -alkoxy- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -hydroxyalkylamino- $C_1$ - $C_4$ -alkyl, amino- $C_1$ - $C_4$ -alkoxy- $C_1$ - $C_4$ -alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy,

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optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy,  
optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy,  
optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-O-,  
5 tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted  
pyridyloxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-  
alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-  
alkylaminocarbonyl, 5-6-membered N-containing  
heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-  
10 C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl,  
aminocarbonyl, 5-6-membered N-containing  
heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino,  
15 preferably unsubstituted or substituted with one  
or more substituents selected from pyridyl,  
phenyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, halo,  
piperidinyl, morpholinyl, methylpiperazinyl,  
methylaminothiocarbonyl, N,N-  
20 diethylaminomethylenyl, N-  
methylaminomethylenyl,  
morpholinylpropylenylaminocarbonyl,  
aminocarbonyl morpholinylpropylenylamino, N,N-  
diethylamino and N,N-  
25 dimethylaminoethylenylamino;

wherein R<sup>9</sup> is selected from optionally substituted  
pyrrolidinyl, optionally substituted piperazinyl,  
optionally substituted piperidinyl, morpholinyl,  
1,4-dioxo-8-aza-spiro[4.5]decyl, pyridyl, phenyl,  
30 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> hydroxyalkyl,  
amino, C<sub>1</sub>-C<sub>2</sub> azidoalkyl, C<sub>1</sub>-C<sub>2</sub> cyanoalkyl, C<sub>1</sub>-C<sub>2</sub>

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aminoalkyl, halo, (optionally substituted pyrrolidinyl)CH<sub>2</sub>-, (optionally substituted piperidinyl)-CH<sub>2</sub>-, (optionally substituted piperazinyl)-CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, (optionally substituted imidazolyl)-CH<sub>2</sub>-, phthalimidyethyl, 5 optionally substituted azepanyl-CH<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-CH<sub>2</sub>-, optionally substituted phenoxy-CH<sub>2</sub>-, C<sub>1</sub>-C<sub>4</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, Boc-aminoethoxymethylenyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy, 15 optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-O-, tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 1-piperidinylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, aminocarbonyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino, 20 preferably 3-(N,N-dimethylamino)-1-pyrrolidinyl, 1-methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, 4-amino-1-piperidinyl, 4-(N-hydroxyethylamino)-1-piperidinyl, 4-(N-propylamino)-1-piperidinyl, 4-(N-benzylamino)-1-piperidinyl, 4-oxo-piperidinyl, 25

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4-(hydroxyimino)-piperidinyl, 4-morpholinyl, 1,4-dioxa-8-aza-spiro[4.5]decyl, pyridyl, phenyl, methyl, ethyl, propyl, amino, azidomethyl, hydroxymethyl, trifluoromethyl, fluoro, chloro, bromo, aminoethyl, aminomethyl, cyanomethyl, 1-pyrrolidinyl-CH<sub>2</sub>-, 2-methoxycarbonyl-1-pyrrolidinyl-CH<sub>2</sub>-, 2-carboxy-1-pyrrolidinyl-CH<sub>2</sub>-, 2-hydroxymethyl-1-pyrrolidinyl-CH<sub>2</sub>-, 1-piperidinyl-CH<sub>2</sub>-, 4-methyl-1-piperidinyl-CH<sub>2</sub>-, 3-methyl-1-piperidinyl-CH<sub>2</sub>-, 2-methyl-1-piperidinyl-CH<sub>2</sub>-, 3,5-dimethyl-1-piperidinyl-CH<sub>2</sub>-, 4-oxo-1-piperidinyl-CH<sub>2</sub>-, 4-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 3-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 2-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-propylamino)-1-piperidinyl-CH<sub>2</sub>-, 1-methyl-4-piperazinyl-CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, (2-methyl-1-imidazolyl)-CH<sub>2</sub>-, 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH<sub>2</sub>-, phthalimidylethylenyl, 1-azepanyl-CH<sub>2</sub>-, 1,4-dioxa-8-aza-spiro[4.5]decyl-CH<sub>2</sub>-, 4-(methyl)phenoxy-methylenyl, 4-(N,N-dimethylaminomethylenyl)phenoxy-methylenyl, methylaminothiocarbonyl, methoxy-methylenyl, ethylaminothiocarbonyl, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminomethylenyl, N-(hydroxypropyl)aminomethylenyl, N-

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ethylaminomethylenyl, Boc-aminoethoxymethylenyl, aminoethoxymethylenyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, 2-pyrrolidinylmethoxy, 1-methyl-2-pyrrolidinylmethoxy, azetidin-3-ylmethoxy, N-Boc-azetidin-3-ylmethoxy, N-Boc-piperidin-4-ylethoxy, 1-methyl-4-piperidinylethoxy, 4-piperidinylethoxy, 4-piperidinylmethoxy, N,N-dimethylaminoethoxy, 3-tetrahydrofuryl-O-, 3-tetrahydrofurylmethoxy, 4-tetrahydrofurylmethoxy, 4-methylphenoxy, 4-(aminoethyl)phenoxy, 4-(1-imidazolyl)phenoxy, 2,4-dimethylphenoxy, phenoxy, 4-cyanophenoxy, 4-[1,3]dioxolan-2-ylphenoxy, 4-fluorophenoxy, 3,4-difluorophenoxy, ethoxycarbonyl, morpholinylpropylenylaminocarbonyl, 1-piperidinylcarbonyl, methylaminocarbonyl, ethylaminocarbonyl, N,N-diethylaminocarbonyl, N-(N',N'-dimethylaminoethylenyl)aminocarbonyl, aminocarbonyl, morpholinylpropylenylamino, N,N-diethylamino, N,N-diethylamino(2-propylenyl)aminomethylenyl, N,N-diethylamino(1-propylenyl)aminomethylenyl and N-(N',N'-dimethylaminoethylenyl)amino;

wherein R<sup>10</sup> is selected from H, hydroxy, and amino; wherein R<sup>11</sup> is selected from pyridyl and pyrimidinyl, preferably pyridyl; and wherein R<sup>12</sup> is selected from H, and C<sub>1</sub>-C<sub>4</sub> alkyl, preferably H, methyl, ethyl and propyl; and pharmaceutically acceptable salts thereof.

A family of specific compounds of particular interest within Formula I' consists of compounds and pharmaceutically-acceptable salts thereof as follows:

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- N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-morpholinylmethyl)pyridinyl]urea;
- Ethyl 1-[6-[3-(2-(pyridin-4-yl)thiazol-4-yl)ureido]-pyridin-2-ylmethyl]-piperidine-4-carboxylate;
- 5 tert-Butyl (1-hydroxymethyl-3-methyl-butyl)-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl)-carbamate;
- 1-[6-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-[6-(3,5-Dimethylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-ylthiazol-4-yl)urea;
- 1-[6-(4-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 15 1-[6-(2-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[2-Pyridin-4-yl-thiazol-4-yl]-3-[6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-pyridin-2-yl]-urea;
- 20 1-[6-(3-Hydroxy-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-[6-(2-Methyl-imidazol-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-[6-Azepan-1-ylmethyl-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 25 1-[6-(4-Hydroxy-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- Ethyl 1-[6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl]piperidine-3-carboxylate;
- 30 Ethyl 1-[6-[3-(2-(pyridin-4-yl)thiazol-4-yl)ureido]-pyridin-2-ylmethyl]piperidine-2-carboxylate;

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- N,N-Diethyl 1-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-ylmethyl)piperidine-3-carboxamide;
- 1-(6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl)-piperidine-3-carboxylic acid;
- 5 Methyl 1-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl)-pyrrolidine-2-carboxylate;
- 1-(6-(3-Methyl-piperidin-1-ylmethyl)-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 10 1-(2-Phenoxy-thiazol-4-yl)-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea;
- tert Butyl 3-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxy)methyl)-azetidine-1-carboxylate;
- 15 tert Butyl 4-(2-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-yloxy)ethyl)piperidine-1-carboxylate;
- 1-(6-(4-Dimethylaminomethyl-phenoxy)methyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 20 1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-(4-methylphenyl)oxymethylpyridin-2-yl)urea;
- tert Butyl (2-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-ylmethoxy)ethyl)carbamate;
- tert Butyl (2-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-3-ylmethoxy)ethyl)carbamate;
- 25 1-(5-Methoxymethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-(5-Morpholin-4-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 30 1-(6-[2-phthalimidylethyl]pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;

- 1-(6-Cyanomethylpyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[2-(2-Chloropyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea;
- 5 1-(6-Aminopyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-(6-Morpholin-4-yl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 10 1-[6-(2,4-Dimethylphenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-(6-Phenoxy-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[6-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 15 1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-p-tolyloxy-pyridin-2-yl)-urea;
- 1-(4-Oxo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-(4-Benzylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 20 1-(4-Propylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 25 1-[4-(2-Hydroxy-ethylamino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-(4-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 30 1-[6-(4-Cyanophenoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;

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- 1-(4-Hydroxyimino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-[6-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-pyridin-2-yl]-3-  
5 (2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-[6-(2-Dimethylamino-ethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 10 1-(2-Methylthiazol-4-yl)-3-(6-phenoxy-pyridin-2-yl)urea;
- 1-[6-(1-Methylpyrrolidin-2-ylmethoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[6-(4-Imidazol-1-yl-phenoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 15 1-(6-Phenoxy-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)urea;
- 1-[6-(4-[1,3]Dioxolan-2-yl-phenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 20 1-[6-(4-Fluorophenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[6-(3,4-Difluorophenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[6-[4-(2-Aminoethyl)phenoxy]pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 25 1-Pyridin-3-yl-3-(2-pyridin-3-yl-thiazol-4-yl)-urea;
- 6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridine-2-carbothioic acid methylamide;
- 1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
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- 1-(6-Methylaminomethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[6-(3-Morpholin-4-yl-propylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 5 1-[6-(2-Dimethylamino-ethylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-(6-Diethylamino-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]nicotinamide;
- 10 4-[4-[3-(6-Propylpyridin-2-yl)ureido]thiazol-2-yl]-benzenesulfonamide;
- tert Butyl (4-{4-[3-(6-Propylpyridin-2-yl)ureido]-thiazol-2-yl}phenyl) carbamate;
- 2-Dimethylaminoethyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridine-2-carboxamide;
- 15 1-[6-(4-Ethylpiperazin-1-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-(2-[4-(4-Morpholinylsulfonyl)phenyl]thiazol-4-yl)-3-(6-propyl-pyridin-2-yl)urea;
- 20 1-[2-(4-Aminophenyl)thiazol-4-yl]-3-(6-propylpyridin-2-yl)urea;
- 1-[6-(4-Benzylpiperazin-1-yl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[6-(4-Methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 25 1-(6-Hydroxymethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- Diethyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridine-2-carboxamide;
- 30 1-[6-(4-Methylpiperazin-1-yl)pyridin-2-yl]-3-(2-pyridin-3-yl-thiazol-4-yl)urea;

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- 1-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridine-2-carboxylic acid ethyl ester;
- 5 1-[6-(Piperidine-1-carbonyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[6-(4-Methylpiperazin-1-yl)pyridin-2-yl]-3-(2-pyrimidin-4-yl-thiazol-4-yl)urea;
- 1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyrimidin-4-yl-thiazol-4-yl)urea;
- 10 1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)urea;
- Methyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridine-2-carboxamide;
- 15 1-[6-(Piperidine-1-carbonyl)pyridin-2-yl]-3-(2-pyridin-3-yl-thiazol-4-yl)urea;
- 1-(6-Ethylaminomethylpyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- Ethyl 6-[3-(2-Pyridin-4-yl-thiazol-4-yl)ureido]pyridine-2-carboxamide;
- 20 Ethyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridine-2-thiocarboxamide;
- 1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(4-pyrimidin-2-yl-piperazin-1-yl)pyridin-2-yl]urea;
- 25 1-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)-urea;
- 1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-pyrrolidin-1-ylmethyl-pyridin-2-yl)-urea;
- 1-[1,6]Naphthyridin-2-yl-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
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- 1-[6-(4-Pyridin-2-yl-piperazin-1-yl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[6-(4-Pyridin-2-yl-piperazin-1-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 5 1-(6-Propyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- 1-(6-Ethyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
- N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-morpholinylmethyl)pyridinyl]urea hydrochloride;
- 10 Ethyl 1-[6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl]-piperidine-4-carboxylate hydrochloride;
- 1-[6-(3,5-Dimethylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-ylthiazol-4-yl)urea hydrochloride;
- 15 1-[6-(4-Oxo-piperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride ;
- 1-[6-(4-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride;
- 20 1-[6-(2-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride ;
- Ethyl 1-[6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl]piperidine-3-carboxylate hydrochloride;
- 25 1-(6-Azepan-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride;
- 1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-piperidin-4-yl-thiazol-4-yl)urea hydrochloride;
- 1-[5-Bromo-2-(pyridin-4-yl)thiazol-4-yl]-3-(6-diethylaminomethyl-pyridin-2-yl)urea
- 30 hydrochloride;

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- Ethyl 1-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl)-piperidine-2-carboxylate hydrochloride;
- N,N-Diethyl 1-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-ylmethyl)piperidine-3-carboxamide hydrochloride;
- 5 1-[6-(Morpholin-4-ylmethyl)-pyridin-2-yl]-3-[(2-pyridin-3-yl)thiazol-4-yl]urea hydrochloride;
- 1-[6-(Azetidin-3-ylmethoxy)pyridin-2-yl]-3-[2-(pyridin-4-yl)thiazol-4-yl]urea;
- 10 1-[6-(2-Piperidin-4-yl-ethoxy)pyridin-2-yl]-3-[2-(pyridin-4-yl)thiazol-4-yl]urea;
- N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-[6-aminopyridin-2-yl]urea;
- 15 1-[2-(2,6-Dichloropyridin-4-yl)thiazol-4-yl]-3-[6-(piperidin-1-ylmethyl)pyridin-2-yl]urea;
- 1-[6-(Piperidin-1-ylmethyl)pyridin-2-yl]-3-[2-[6-(2,2,2-trifluoroethoxy)pyridin-3-yl]thiazol-4-yl]urea;
- 20 1-[6-(2-Methylimidazol-1-ylmethyl)pyridin-2-yl]-3-[2-(pyridin-3-yl)thiazol-4-yl]urea;
- 1-[6-(Morpholin-4-ylmethyl)-pyridin-2-yl]-3-[(2-pyridin-3-yl)thiazol-4-yl]urea;
- 1-(6-[3-(2-(4-Pyridinyl)-4-thiazolyl)ureido]-pyridin-2-ylmethyl)-piperidine-4-carboxylic acid;
- 25 1-[6-[(1-Hydroxymethyl-3-methylbutylamino)methyl]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-[6-(4-Oxo-piperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 30 1-[6-[4-(Propylamino)piperidin-1-ylmethyl]pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;

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- 1-{6-[4-(2-Hydroxyethylamino)piperidin-1-ylmethyl]-  
pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;  
N-(6-Aminomethyl-2-pyridyl)-N'-[2-(4-pyridinyl)-4-  
thiazolyl]urea;
- 5 1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-piperidin-4-  
yl-thiazol-4-yl)urea;  
1-[5-Bromo-2-(pyridin-4-yl)thiazol-4-yl]-3-(6-  
diethylaminomethyl-pyridin-2-yl)urea;  
1-{6-[(3-Hydroxypropylamino)methyl]-pyridin-2-yl]-3-(2-  
pyridin-4-yl-thiazol-4-yl)urea;
- 10 1-[6-(2-Hydroxymethylpyrrolidin-1-ylmethyl)-pyridin-2-  
yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;  
1-{6-[3-(2-Pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-  
ylmethyl}-pyrrolidine-2-carboxylic acid;
- 15 1-(5-Bromo-(2-pyridin-4-yl)thiazol-4-yl)-3-(6-  
methylpyridin-2-yl)urea;  
4-{4-[3-(6-Propyl-pyridin-2-yl)-ureido]-thiazol-2-yl}-  
benzenesulfonamide;  
1-(2-[4-(4-Morpholinylsulfonyl)phenyl]thiazol-4-yl)-3-  
20 (6-propylpyridin-2-yl)urea;  
tert-Butyl 4-{4-[3-(6-propylpyridin-2-yl)ureido]-  
thiazol-2-yl}phenyl carbamate;  
1-[2-(4-Aminophenyl)thiazol-4-yl]-3-(6-propylpyridin-2-  
yl)urea;
- 25 1-{6-[2-(1-Methylpiperidin-4-yl)ethoxy]pyridin-2-yl]-3-  
(2-pyridin-4-yl-thiazol-4-yl)urea;  
1-[6-(2-Aminoethoxymethyl)pyridin-2-yl]-3-(2-pyridin-4-  
yl-thiazol-4-yl)urea;  
1-[5-(2-Aminoethoxymethyl)pyridin-2-yl]-3-(2-pyridin-4-  
30 yl-thiazol-4-yl)urea;

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- 1-{6-[2-Aminoethyl]pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 1-{6-[2-(N,N-Dimethylamino)ethyl]pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea;
- 5 1-[2-(2-Ethoxyppyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(2-Methoxyppyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(2-Ethoxyppyridin-4-yl)thiazol-4-yl]-3-(6-ethyl-pyridin-2-yl)urea;
- 10 1-[2-(6-Methoxyppyridin-3-yl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-(2-Bromothiazol-4-yl)-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 15 1-[2-(4-Methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-(2-Benzo[1,3]dioxol-5-yl-thiazol-4-yl)-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea;
- 1-[2-(3,4-Dimethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 20 1-[2-(4-Fluorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(3-Ethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 25 1-[2-(3-Aminophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(4-Trifluoromethylophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(3-Trifluoromethylophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
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- 1-[2-(3-Fluorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(4-Dimethylaminophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 5 1-[2-phenylthiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(4-Aminophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(3,5-Dichlorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 10 1-[2-(2,4-Difluorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(3,4-Dichlorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 15 1-[2-(2,4-Dimethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(1H-Indol-5-yl)-thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea;
- 1-[2-(4-Methylthiophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 20 1-[2-(4-Cyanophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(3-Methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 25 1-[2-(2-Methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(3-Hydroxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
- 1-[2-(4-Methoxyphenoxyethyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;
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- 1-(6-[(2-Diethylamino-1-methylethylamino)methyl]-  
pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;  
4-{4-[3-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-ureido]-  
thiazol-2-yl}-benzenesulfonamide;
- 5 Ethyl 2-[3-[2-(pyridin-4-yl)-thiazol-4-yl]ureido]-  
thiazole-4-carboxylate;
- 1-(4-Cyclohexylthiazol-2-yl)-3-[2-(pyridin-4-yl)-  
thiazol-4-yl]urea;
- 1-(Pyridin-3-ylmethyl)-3-(2-pyridin-4-yl-thiazol-4-  
yl)urea;
- 10 1-(Pyridin-2-ylmethyl)-3-(2-pyridin-4-yl-thiazol-4-  
yl)urea;
- 1-[6-(Piperidin-1-ylmethyl)pyridin-2-yl]-3-(3-  
pyridin-3-yl-phenyl)urea;
- 15 1-(3-Hydroxy-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-  
yl)-urea;
- 1-(3-Amino-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-  
yl)-urea;
- 1-(3-Hydroxy-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-  
yl)-urea;
- 20 1-(3-Amino-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-  
yl)-urea;
- 1-(3-Piperidin-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-  
yl-thiazol-4-yl)-urea;
- 25 (1-Diethylaminomethyl-2-methyl-propyl)-(6-[3-(2-  
pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-  
ylmethyl)-carbamic acid tert-butyl ester;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-  
diethylaminomethylamino)pyridinyl]urea;
- 30 N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-[3-(1-  
morpholinyl)propyl]amino]pyridinyl]urea;

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- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-[4-(3-pyridinyl)-2-thiazolyl] urea;
- N-[3-(3-pyridinyl)phenyl]-N'-2-(6-propylpyridinyl)urea;
- N-[3-(4-pyridinyl)phenyl]-N'-2-(6-propylpyridinyl)urea;
- 5 N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-(5-methylpyridinyl)urea;
- N,N'-bis [2-(3-pyridinyl)-4-thiazolyl] urea;
- N,N'-bis [2-(4-pyridinyl)-4-thiazolyl] urea;
- N-[2-(3-pyridinyl)-4-thiazolyl]-N'-[4-(3-pyridinyl)-2-thiazolyl] urea;
- 10 N-[2-(3-pyridinyl)-4-thiazolyl]-N'-2-thiazolylurea ;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-thiazolylurea ;
- N-[2-(3-pyridinyl)-4-thiazolyl]-N'-4-phenyl-2-thiazolylurea ;
- 15 N-[2-(3-pyridinyl)-4-thiazolyl]-N'-2-phenyl-4-thiazolylurea ;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-phenyl-4-thiazolylurea ;
- N-[2-(3-pyridinyl)-4-thiazolyl]-N'-2-pyridinylurea ;
- 20 N-[2-(3-pyridinyl)-4-thiazolyl]-N'-3-pyridinylurea ;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-thiazolylurea ;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-pyridinylurea ;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-benzthiazolylurea;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-[2-(3-pyridinyl)-4-thiazolyl] urea ;
- 25 N-[2-(4-pyridinyl)-4-thiazolyl]-N'-[4-(3-pyridinyl)-2-thiazolyl] urea;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-quinolinyurea;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-3-quinolinyurea;
- 30 N-[2-(4-pyridinyl)-4-thiazolyl]-N'-4-benzimidazolylurea;

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- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-(5-trifluoromethylpyridinyl)urea;
- 5 N-[2-methyl-4-thiazolyl]-N'-2-pyridinylurea  
N-[2-methyl-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea;  
N-[2-(3-pyridinyl)-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea;
- N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea;
- 10 N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-(6-methylpyridinyl)urea;  
N-[2-(3-pyridinyl)-4-thiazolyl]-N'-2-(6-methylpyridinyl)urea;
- 15 N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-(5-methylpyridinyl)urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-(3-methylpyridinyl)urea;
- 20 N-[2-(4-pyridinyl)-4-thiazolyl]-N'-[5-(1,1-dimethylethyl)-3-isoxazolyl]urea;  
N-[2-(2-thienyl)-4-thiazolyl]-N'-2-pyridinylurea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-(6-bromopyridinyl)urea;
- 25 N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-(6-chloropyridinyl)urea;  
N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea;
- 30 N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea;

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- N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-pyridinylurea;  
N,N'-bis [2-(4-pyridinyl)-4-thiazolyl]-N'-methylurea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-pyridinyl-N'-  
methylurea;
- 5 [4-[(1-piperidylcarbonyl)amino]-2-thiazolyl]-4-  
pyridine;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(1-  
piperdinyl)pyridinyl]urea;  
N-[2-(2-ethyl-4-pyridinyl)-4-thiazolyl]-N'-2-(6-  
10 propylpyridinyl)urea;  
[[2-(4-pyridinyl)-4-thiazolylamino]carbonyl]amino]-6-  
pyridinyl-2-carboxylic acid;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(4-  
morpholinyl)pyridinyl]urea;
- 15 N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(1-methyl-4-  
piperazinyl)pyridinyl]urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(N"-  
methylaminothiocarbonyl)pyridinyl]urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-  
20 dimethylaminomethyl)pyridinyl]urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(N"-  
methylaminomethyl)pyridinyl]urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-3-(1-  
bromoisquinolinyl)urea;
- 25 N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[[3-(1-  
morpholinyl)propyl]aminocarbonyl]pyridinyl]urea;  
N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-(4,6-  
dimethylpyridinyl)urea;  
N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-(4-  
30 methylpyridinyl)urea;

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- N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-(5-methylpyridinyl)urea;  
N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea;  
5 N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-(3-methylpyridinyl)urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-3-[(1-morpholinyl)propyl]-N'-6-(2-aminopyridinyl)urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-[3-(1-morpholinyl)propylamino]pyridinyl]urea;  
10 N-[2-(2-pyridinyl)-4-thiazolyl]-N'-2-(6-methylbenzthiazolyl)urea;  
N-[2-(2-thienyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea;  
15 N-[2-(2-thienyl)-4-thiazolyl]-N'-2-(3-methylpyridinyl)urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-dimethylaminoethylamino)pyridinyl]urea;  
N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-diethylamino)pyridinyl]urea; and  
20 [[2-(4-pyridinyl)-4-thiazolylamino]carbonyl]amino]-6-pyridinyl-3-carboxamide.

#### Indications

- 25 Compounds of the present invention would be useful for, but not limited to, the treatment of cell proliferative diseases or of apoptosis.

- The compounds of the invention are endowed with kinase inhibitory activity, such as CDK/cyclin kinase  
30 inhibitory activity and KDR inhibitory activity.

The compounds of the invention are useful in therapy as antineoplasia agents.

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Compounds of the invention would be useful for the treatment of neoplasia including cancer, including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including  
5 small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocytic leukemia, acute  
10 lymphoblastic leukemia, B-cell lymphoma, T-cell- Lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias,  
15 myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma,  
20 glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma).

Preferably, the compounds are useful for the  
25 treatment of neoplasia selected from lung cancer, colon cancer and breast cancer.

Due to the key role of CDKs in the regulation of cellular proliferation, these compounds are also useful in the treatment of a variety of cell  
30 proliferative disorders such as, for instance, blood vessel proliferative disorders including arthritis and

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restenosis; fibrotic disorders including hepatic cirrhosis and atherosclerosis; mesangial cell proliferative disorders including glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection and glomerulopathies; metabolic disorders including psoriasis, diabetes mellitus, chronic wound healing, inflammation, and diabetic retinopathy and other vision disorders; and others including benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, pulmonary fibrosis, angiogenesis, metastasis, vascular smooth cell proliferation, post-surgical stenosis and hypertrophic scar formation, eczema, inflammatory bowel disease, endotoxic shock, and fungal infections.

The compounds of the invention are useful to prevent the phosphorylation of tau protein.

The compounds of the invention are useful in the treatment of neurological disorders, including neurological injuries and neurodegenerative diseases, such as, but not limited to, stroke, brain trauma, epilepsy, spinal cord injury, ischemia, multiple sclerosis, vision related disorders including but not limited to glaucoma and macular degeneration, hearing loss, AIDS-related dementia, retinitis pigmentosa, spinal muscular atrophy, cerebellar degeneration, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease and Alzheimer's disease.

Compounds of formula I, as inhibitors of the CDKs, can modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in

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the treatment of viral infections, including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus.

5       The compounds of this invention may also act as inhibitors of other protein kinases, e.g. KDR, IKK, JNK3, and thus be effective in the treatment of diseases associated with other protein kinases.

      Besides being useful for human treatment, these  
10    compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

      Inhibitors of certain kinases may have utility in  
15    the treatment of diseases when the kinase is not misregulated, but is nonetheless essential for maintenance of the disease state. In this case, inhibition of the kinase activity would act either as a cure or palliative for these diseases. For example,  
20    many viruses, such as human papilloma virus; disrupt the cell cycle and drive cells into the S-phase of the cell cycle. Preventing cells from entering DNA synthesis after viral infection by inhibition of essential S-phase initiating activities such as CDK2,  
25    may disrupt the virus life cycle by preventing virus replication. This same principle may be used to protect normal cells of the body from toxicity of cycle-specific chemotherapeutic agents. Inhibition of CDK2 or CDK4 will prevent progression into the cycle  
30    in normal cells and limit the toxicity of cytotoxics which act in S-phase, G2 or mitosis. Furthermore,

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CDK2/cyclin E activity has also been shown to regulate NF- $\kappa$ B: Inhibition of CDK2 activity stimulates NF- $\kappa$ B-dependent gene expression, an event mediated through interactions with the p300 coactivator. NF- $\kappa$ B regulates

5 genes involved in inflammatory responses, (such as hematopoietic growth factors chemokines and leukocyte adhesion molecules) and may be involved in the suppression of apoptotic signals within the cell. Thus, inhibition of CDK2 may suppress apoptosis

10 induced by cytotoxic drugs via a mechanism which involves NF- $\kappa$ B. Inhibition of CDK2 activity may also have utility in other cases where regulation of NF- $\kappa$ B plays a role in etiology of disease. A further example may be taken from fungal infections: Inhibition of the

15 *Aspergillus* kinases Cdc2/CDC28 or Nim A may cause arrest or death in the fungi, improving the therapeutic outcome for patients with these infections.

The compounds of the invention are useful as

20 modulators of apoptosis. As such they are useful in the prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis and

25 autoimmune diabetes mellitus), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, vision related disorders including but not limited to glaucoma and macular degeneration,

30 arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases

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(including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis) aspirin-sensitive rhinosinusitis, cystic  
5 fibrosis, kidney diseases and cancer pain.

#### Definitions

The term "prevention" includes either preventing the onset of disorders altogether or  
10 delaying the onset of a preclinically evident stage of disorders in individuals. This includes prophylactic treatment of those at risk of developing a disease, such as a cancer, for example.

15 The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically  
20 associated with alternative therapies. For example, effective neuroplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly-proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm. Alternatively,  
25 effective therapeutic agents for the treatment of neurological disorders minimize the damage from injury, improve cognitive functions, and the like.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom  
30 to form a hydroxyl radical.

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Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. Even more preferred are lower alkyl radicals having one to four carbon atoms. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about four

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carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

- 5       The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have
- 10   either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred
- 15   are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl,
- 20   difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.
- 25   The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one
- 30   to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl,

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hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embrace linear or branched oxy-  
5 containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include , methoxy, ethoxy, propoxy, butoxy and tert-butoxy. Even  
10 more preferred are lower alkoxy radicals having one to three carbon atoms. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy  
15 radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a  
20 carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. More preferred  
25 aryl is phenyl. Said "aryl" group may have 1 to 3 substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino.

The term "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-  
30 containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It

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does not include rings containing -O-O-, -O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as hydroxyl, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino and lower alkylamino.

- Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl];
- 10 saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl].
- 15 Examples of partially saturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

- Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated
- 20 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 3 to 6-membered
- 25 heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.;
- 30 unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen

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atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals:

10 unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed

15 heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl].

20 benzothiadiazolyl].

The term also includes bridged, spiro and oxo-containing heterocyclic rings, such as 1,4-dioxo-8-aza-spiro[4.5]decyl, phthalimidyl, 1,4-dioxo-8-aza-spiro[4.5]decyl, and (1-aza-bicyclo[2.2.2]oct-3-yl).

25 Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include quinolyl, isoquinolyl, imidazolyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. Even more preferred

30 heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from sulfur

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nitrogen and oxygen, selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

5       The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals  $-SO_2-$ .

          The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," whether alone or used with terms such  
10 as "N-alkylaminosulfonyl", "N-arylamino sulfonyl", "N,N-dialkylaminosulfonyl" and "N-alkyl-N-arylamino sulfonyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ( $-SO_2NH_2$ ).

15       The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" and "N,N-dialkylaminosulfonyl" where sulfamyl radicals are substituted, respectively, with one alkyl radical, or two alkyl radicals. More preferred alkylaminosulfonyl radicals are "lower  
20 alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, N-ethylaminosulfonyl and N-methyl-  
25 N-ethylaminosulfonyl.

          The terms "N-arylamino sulfonyl" and "N-alkyl-N-arylamino sulfonyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical. More preferred N-alkyl-  
30 N-arylamino sulfonyl radicals are "lower N-alkyl-N-arylsulfonyl" radicals having alkyl radicals of one to

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six carbon atoms. Even more preferred are lower N-alkyl-N-arylsulfonyl radicals having one to three carbon atoms. Examples of such lower N-alkyl-N-arylaminosulfonyl radicals include N-methyl-N-phenylaminosulfonyl and N-ethyl-N-phenylaminosulfonyl. Examples of such N-aryl-aminosulfonyl radicals include N-phenylaminosulfonyl.

The term "arylkylaminosulfonyl" embraces aralkyl radicals as described above, attached to an aminosulfonyl radical. More preferred are lower arylalkylaminosulfonyl radicals having one to three carbon atoms.

The term "heterocyclylamino sulfonyl" embraces heterocyclyl radicals as described above, attached to an aminosulfonyl radical.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes  $\text{-CO}_2\text{H}$ .

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes  $\text{-(C=O)-}$ .

The term "aminocarbonyl" when used by itself or with other terms such as "aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylamino carbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylamino carbonyl", "N-alkyl-N-hydroxyaminocarbonyl" and "N-alkyl-N-hydroxyaminocarbonylalkyl", denotes an amide group of the formula  $\text{-C(=O)NH}_2$ .

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals which have been substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred

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are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

The terms "N-arylaminoalkyl" and "N-alkyl-N-arylaminoalkyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals.

10 The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term includes both mono- and di-substituted amines. Even more preferred are lower alkylaminoalkyl radicals having one to three carbon atoms.

The term "heterocyclylalkyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkyl radicals are "5- or 6-membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

25 The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are lower aralkyl radicals phenyl attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl,

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diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "arylalkenyl" embraces aryl-substituted alkenyl radicals. Preferable arylalkenyl radicals are "lower arylalkenyl" radicals having aryl radicals attached to alkenyl radicals having two to six carbon atoms. Examples of such radicals include phenylethenyl. The aryl in said arylalkenyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "arylalkynyl" embraces aryl-substituted alkynyl radicals. Preferable arylalkynyl radicals are "lower arylalkynyl" radicals having aryl radicals attached to alkynyl radicals having two to six carbon atoms. Examples of such radicals include phenylethynyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH<sub>3</sub>S-).

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower haloalkylthio radicals having one

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to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one  
5 to ten carbon atoms, attached to a divalent  $-S(=O)-$  atom. More preferred are lower alkylsulfinyl radicals having one to three carbon atoms.

The term "arylsulfinyl" embraces radicals containing an aryl radical, attached to a divalent  $-S(=O)-$  atom. Even more preferred are optionally  
10 substituted phenylsulfinyl radicals.

The term "haloalkylsulfinyl" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent  $-S(=O)-$  atom. Even more  
15 preferred are lower haloalkylsulfinyl radicals having one to three carbon atoms.

The term "alkylamino" denotes amino groups which have been substituted with one alkyl radical and with two alkyl radicals, including terms "N-alkylamino" and  
20 "N,N-dialkylamino". More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable  
25 "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals,  
30 such as N-phenylamino. The "arylamino" radicals may be

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further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C<sub>1</sub>-C<sub>3</sub>-alkylamino radicals, such as N-benzylamino. The "aralkylamino" radicals may be further substituted on the aryl ring portion of the radical.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C<sub>1</sub>-C<sub>3</sub>-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are

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"lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

The term "cycloalkenyl" includes carbocyclic groups have one or more carbon-carbon double bonds. "Cycloalkenyl" and "cycloalkyldienyl" compounds are included. Preferred cycloalkenyl groups include C<sub>3</sub>-C<sub>6</sub> rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

The present invention preferably includes compounds that selectively inhibit CDK2 and/or CDK5.

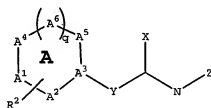
The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of a cell proliferation or apoptosis mediated disease state, including those described previously. The compounds of the present invention are also useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of CDKs and other kinases. The compounds of the present invention are also useful in the manufacture of a medicament to treat neurological disorders.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective

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amount of a compound of Formulas I-V in association with a least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of  
 5 treating cell proliferative disorders, apoptosis mediated disorders, cancer, CDK mediated disorder or neurological disorders, in a subject, the method comprising treating the subject having or susceptible to such disorder with a therapeutically-effective  
 10 amount of a compound of Formula I



wherein each of A<sup>1</sup>-A<sup>6</sup> is selected from CH<sub>2</sub>, CH, C, O, S,  
 15 NH and N; wherein A<sup>1</sup>-A<sup>6</sup> together form a ring A selected from

additionally substituted or unsubstituted 5- or 6-membered heterocyclyl,  
 additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group,  
 20 additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, and  
 additionally substituted or unsubstituted phenyl,  
 wherein the ring A is additionally substituted  
 25 with one or more substituents independently selected from halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>, cycloalkyl, optionally substituted

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phenylalkylenyl, optionally substituted 5-6  
membered heterocyclyl, optionally substituted  
heteroarylalkylenyl, optionally substituted  
phenyl, lower alkyl, cyano, lower hydroxyalkyl,  
5 nitro, lower alkenyl, lower alkynyl and lower  
haloalkyl;

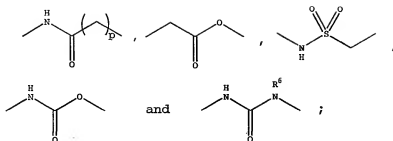
wherein X and Z taken together form a nitrogen  
containing ring selected from  
unsubstituted 5-6 membered heterocyclyl,  
10 unsubstituted 5-6 membered heterocyclyl fused with a  
phenyl group,  
5-6 membered heterocyclyl substituted with one or  
more substituents independently selected from R<sup>1</sup>,  
and

15 5-6 membered nitrogen-containing heterocyclyl, fused  
with a phenyl group, substituted with one or more  
substituents independently selected from R<sup>1</sup>;

wherein R<sup>1</sup> is independently selected from H, halo, -  
OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -CONR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>,  
20 -C(S)NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>,  
cycloalkyl, optionally substituted phenylalkylenyl,  
optionally substituted 4-10 membered heterocyclyl,  
optionally substituted 4-10 membered  
heterocyclylalkyl, optionally substituted phenyl,  
25 optionally substituted phenoxy, lower alkyl, lower  
cyano, lower alkenyl, lower alkynyl and lower  
haloalkyl;

wherein Y is selected from, in either orientation,

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wherein  $\text{R}^2$  is selected from

lower alkylaminoalkynyl,

5 substituted or unsubstituted phenyl,

substituted or unsubstituted 5-6 membered

heterocyclyl, and

substituted or unsubstituted 5-6 membered

heterocyclyl bridged with a phenyl group;

10 wherein substituted  $\text{R}^2$  is substituted with one or

more substituents independently selected from

halo,  $-\text{OR}^3$ ,  $-\text{SR}^3$ ,  $-\text{CO}_2\text{R}^3$ ,  $-\text{CO}_2\text{NR}^3\text{R}^3$ ,  $-\text{COR}^3$ , -

$\text{NR}^3\text{R}^3$ ,  $-\text{C}(\text{O})\text{NR}^3\text{R}^3$ ,  $-\text{SO}_2\text{NR}^3\text{R}^3$ ,  $-\text{NR}^3\text{C}(\text{O})\text{OR}^3$ , -

$\text{NHC}(\text{O})\text{R}^3$ ,  $-\text{SO}_2\text{NHC}(\text{O})\text{R}^3$ ,  $-\text{C}(\text{S})\text{NR}^3\text{R}^3$ , nitro, -

15 cycloalkyl, optionally substituted

phenylalkylenyl, optionally substituted 4-7

membered heterocyclyl, optionally substituted

heterocyclylalkylenyl, optionally substituted

phenyl, optionally substituted

20 phenoxyalkylenyl, optionally substituted

heterocycliloxyalkyl, lower alkyl, cyano, lower

hydroxyalkyl, lower alkoxyalkyl, lower

azidoalkyl, lower aminoalkyl, lower

(hydroxyalkyl)aminoalkyl, lower

25 alkylaminoalkyl, lower alkylaminoalkoxy, lower

aminoalkoxyalkyl, lower (alkylaminoalkyl)amino

lower ((alkylamino)alkylamino)alkyl, lower

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alkylaminoalkylaminocarbonyl, lower cyanoalkyl,  
lower alkenyl, lower alkynyl and lower  
haloalkyl;

wherein R<sup>3</sup> is selected from H, lower alkyl, optionally

5 substituted phenyl, optionally substituted  
phenylalkyl, optionally substituted heterocyclyl,  
optionally substituted heterocyclylalkyl, C<sub>3</sub>-C<sub>6</sub>  
cycloalkyl, and lower haloalkyl;

wherein R<sup>6</sup> is selected from H, alkyl, 5-6 membered

10 heterocyclylalkylenyl and alkylamino;

wherein p is 1 or 2; and

wherein q is 0 or 1;

and pharmaceutically acceptable salts thereof;

provided A is not thiazol-2-yl when Y is ureido.

15

#### COMBINATIONS

While the compounds of the invention can be  
administered as the sole active pharmaceutical agent,  
they can also be used in combination with one or more  
20 compounds of the invention or other agents. When  
administered as a combination, the therapeutic agents  
can be formulated as separate compositions that are  
administered at the same time or sequentially at  
different times, or the therapeutic agents can be  
25 given as a single composition.

The phrase "co-therapy" (or "combination-therapy"),  
in defining use of a compound of the present invention  
and another pharmaceutical agent, is intended to  
embrace administration of each agent in a sequential  
30 manner in a regimen that will provide beneficial  
effects of the drug combination, and is intended as

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well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

5       Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic  
10 agents.

      If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formula I may also be administered sequentially with known anticancer  
15 or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of formula I may be administered either prior to or after administration of the known anticancer or cytotoxic agent.

20       Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents or microtubule  
25 poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia etc... Experiments performed in *in vivo* animal models and in *in vitro* cell  
30 based assays have demonstrated that combining chemotherapeutic agents with cell cycle inhibitors,

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such as CDK inhibitors, typically results in either decreased rate of tumor growth or, in some cases, tumor regression. Combining chemotherapy with a CDK inhibitor typically results in an increased therapeutic index and  
5 lower levels of both agents are required. This ultimately results in a decrease in toxicity and an increase in efficacy.

Schwartz et al, Clin. Can. Res., 3,1467-1472 (1997) have demonstrated that combining the CDK  
10 inhibitor flavopiridol with mitomycin-C (DNA alkylating agent) resulted in an increased rate of apoptosis in gastric and breast cancer cells. Bible et al (Bible et al., Cancer Res., 57, 3375-3380 (1997) have also demonstrated therapeutic synergy exists between  
15 flavopiridol and paclitaxel, cytarabine, topotecan, doxorubicin, and etoposide (all standard chemotherapeutic agents) when tested in cell based assays using human non-small cell lung cancer cells. Preclinical models (cell culture) suggest that a cell  
20 cycle inhibitor potentiates the effect of a cytotoxic agent when administered after the chemotherapeutic agent. The chemotherapeutic agent will induce specific DNA/mitotic damage checkpoints in normal cells which in combination with a CDK inhibitor will cause a cell  
25 cycle arrest or cytostatic effect. In contrast, tumor cells will be driven into apoptosis or cell death when a chemotherapeutic agent and a CDK inhibitor are combined due to tumor cells attempting to activate defective DNA damage and cell cycle checkpoints. In  
30 addition, scheduling of a CDK inhibitor for clinical trials should include a rest period to allow the

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patients normal cells to recover and reduce the potential for cytotoxic side effects.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and  
5 in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents,  
10 hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antimetabolite-type/thymidilate  
15 synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiaazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694,  
20 cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine  
25 phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-  
30 39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-

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AC, Takeda TAC-788, thioguanine, tiazaofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT and uricytin.

- A second family of antineoplastic agents which may
- 5 be used in combination with compounds of the present invention consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide
- 10 analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa
- 15 D-19-384, Sumimoto DACHP(My<sub>2</sub>), diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam,
- 20 ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromustine, Tanabe
- 25 Seiyaku TA-077, taumustine, temozolomide, teroxirone, tetraplatin and trimelamol.

- A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antibiotic-type antineoplastic
- 30 agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group

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- consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A,
- 5 bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin,
- 10 daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb,
- 15 Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kzasumycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-20 5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin,
- 25 pilatin, pirarubicin, porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS 30 Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine,

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tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of  $\alpha$ -carotene,  $\alpha$ -difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphetamine, amacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin, glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BM-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clafenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytosine, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel elliprabin, elliptinium acetate, Tsumura EPMTTC, the epothilones, ergotamine, etoposide, etretinate, fenretinide,

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- Fujisawa FR-57704, gallium nitrate, genkwadaphnin,  
Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N,  
hexadecylphosphocholine, Green Cross HO-221,  
homoharringtonine, hydroxyurea, BTG ICRF-187,  
5 ilmofofosine, isoglutamine, isotretinoin, Otsuka JI-36,  
Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM,  
MECT Corp KI-8110, American Cyanamid L-623,  
leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-  
186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048,  
10 Medco MEDR-340, merbarone, merocyanine derivatives,  
methylanilinoacridine, Molecular Genetics MGI-136,  
minactivin, mitonafide, mitouidone mopidamol,  
motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino  
acids, Nisshin Flour Milling N-021, N-acylated-  
15 dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole  
derivative, Normosang, NCI NSC-145813, NCI NSC-361456,  
NCI NSC-604782, NCI NSC-95580, ocreotide, Ono ONO-112,  
oquizanocine, Akzo Org-10172, paclitaxel,  
pancratistatin, pazelliptine, Warner-Lambert PD-111707,  
20 Warner-Lambert PD-115934, Warner-Lambert PD-131141,  
Pierre Fabre PE-1001, ICRT peptide D, piroxantrone,  
polyhaematoporphyrin, polypreic acid, Efamol porphyrin,  
probitane, procabazine, proglumide, Invitron protease  
nexin I, Tobishi RA-700, razoxane, Sapporo Breweries  
25 RBS, restrictin-P, retelliptine, retinoic acid, Rhone-  
Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline  
SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm  
SP-10094, spatol, spirocyclopropane derivatives,  
spirogermanium, Unimed, SS Pharmaceutical SS-554,  
30 stypoldinone, Stypoldione, Suntory SUN 0237, Suntory  
SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-

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680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, 5 vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM-534.

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic 10 agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANKER, ancerim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, 15 broxuridine, capecitabine, celecoxib, celmoleukin, cetorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, 20 doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, 25 exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zoigamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, 30 human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon

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- alfa, natural, interferon alfa-2, interferon alfa-2a,  
interferon alfa-2b, interferon alfa-N1, interferon  
alfa-n3, interferon alfacon-1, interferon alpha,  
natural, interferon beta, interferon beta-1a,  
5 interferon beta-1b, interferon gamma, natural  
interferon gamma-1a, interferon gamma-1b, interleukin-  
1 beta, iobenguane, irinotecan, irsogladine,  
lanreotide, LC 9018 (Yakult), leflunomide,  
lenograstim, lentinan sulfate, letrozole, leukocyte  
10 alpha interferon, leuprorelin, levamisole +  
fluorouracil, liarozole, lobaplatin, lonidamine,  
lovastatin, masoprocol, melarsoprol, metoclopramide,  
mifepristone, miltefosine, mirimostim, mismatched  
double stranded RNA, mitoguazone, mitolactol,  
15 mitoxantrone, molgramostim, nafarelin, naloxone +  
pentazocine, nartograstim, nedaplatin, nilutamide,  
noscapine, novel erythropoiesis stimulating protein,  
NSC 631570 octreotide, oprelvekin, osaterone,  
oxaliplatin, paclitaxel, pamidronic acid,  
20 pegaspargase, peginterferon alfa-2b, pentosan  
polysulfate sodium, pentostatin, picibanil,  
pirarubicin, rabbit antithymocyte polyclonal antibody,  
polyethylene glycol interferon alfa-2a, porfimer  
sodium, raloxifene, raltitrexed, rasburicase, rhenium  
25 Re 186 etidronate, RII retinamide, rituximab,  
romurtide, samarium (153 Sm) lexidronam, sargramostim,  
sizofiran, sobuzoxane, sonermin, strontium-89  
chloride, suramin, tasonermin, tazarotene, tegafur,  
temoporfin, temozolomide, teniposide,  
30 tetrachlorodecaoxide, thalidomide, thymalfasin,  
thyrotropin alfa, topotecan, toremifene, tositumomab-

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- iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine,
- 5 valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid;
- abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminoglutethimide,
- 10 diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine
- 15 dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic
- 20 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein,
- 25 pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin,
- 30 tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan

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Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Alternatively, the present compounds may also be  
5 used in co-therapies with other anti-neoplastic agents, such as other kinase inhibitors including KDR inhibitors, p38 inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors, NSAID's, SOD mimics or  $\alpha_v\beta_3$  inhibitors.

10 Alternatively, the present compounds may also be used in co-therapies with other treatments for neurological treatments such as thrombolytic and anticoagulant agents including tPA, urokinase and inhibitors of platelet aggregation, p38 inhibitors,  
15 IL1ra, NMDA inhibitors, antiparkinsonian agents including carbidopa and levodopa, and inhibitors of lipid peroxidation, for example.

The present invention comprises a process for the preparation of a compound of Formula I-V.

20 Compounds of the present invention can possess, in general, one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be  
25 obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric,  
30 dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the

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mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Compounds of the present invention can possess, in general, tautomeric forms, which are included in the family of compounds in Formula I.

Also included in the family of compounds of Formula I-V are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I-V may be prepared from an inorganic acid or from an organic acid. Examples of

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- such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic,
- 5 heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic,
- 10 glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic,
- 15 camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxyethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-
- 20 phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic,  $\beta$ -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I-V include
- 25 metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine,
- 30 arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl

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morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate  
5 acid or base with the compound of Formula I-V.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl,  
10 diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby  
15 obtained.

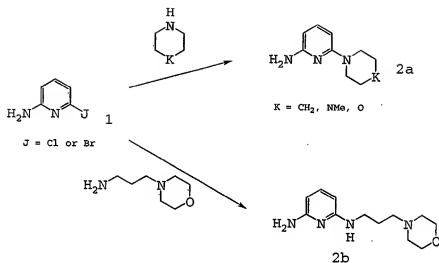
Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as  
20 oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Additional examples of such salts can be found in  
25 Berge et al., J. Pharm. Sci., 66, 1 (1977).

### GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized  
30 according to the following procedures of Schemes 1-17, wherein the substituents are as defined for Formulas I-V, above, except where further noted.

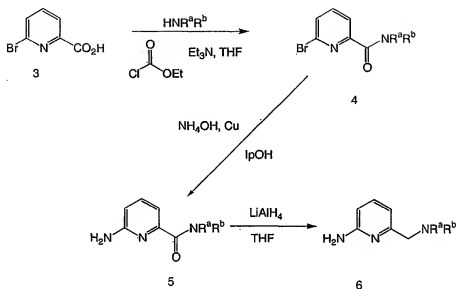
## Scheme 1



- 5            Substituted pyridines can be prepared according to the method set out in Scheme 1. A mixture of halo-
- aniline **1**, substituted amine and phenol was reacted, preferably at a temperature above RT and more
- preferably at temperature of about 150°C, to yield the
- 10       heterocyclyl derivative **2a** or substituted amine derivative **2b**.

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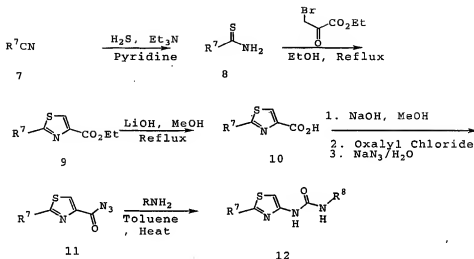
## Scheme 2



- 5 Substituted pyridines can be prepared according to the method set out in Scheme 2. A halopicolinic acid 3 is reacted with substituted amines (where  $\text{R}_a$  and  $\text{R}_b$  are H, alkyl, substituted alkyl, etc.) in the presence of chloroformate esters and base in a suitable solvent to form the halopyridyl amide derivatives 4. Preferably the reaction is at a temperature below RT, more preferably the reaction occurs at a temperature of about  $0^\circ\text{C}$ . The halopyridyl amide 4 is dehalogenated, such as with  $\text{NH}_4\text{OH}$  and  $\text{Cu}$  powder in an appropriate solvent, such as  $\text{IpOH}$  to form the aniline derivative 5. Preferably the reaction occurs at a temperature above RT, more preferably the reaction occurs at about  $100^\circ\text{C}$ . The aniline derivative 5 is reduced, such as with  $\text{LiAlH}_4$  in  $\text{Et}_2\text{O}$  to form the aminoalkyl derivative 6.

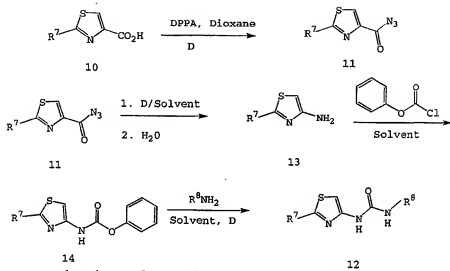
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## Scheme 3



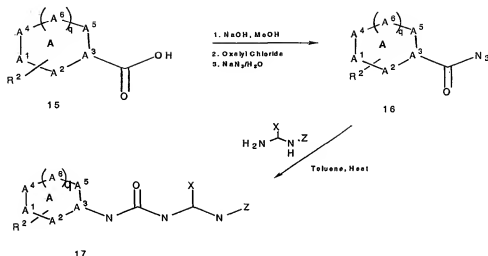
- 5 Substituted 4-thiazolylurea compounds 12 are prepared from the corresponding nitriles 7 according to the method set out in Scheme 3. Substituted nitriles 7 are added to base at about RT and  $H_2S$  is bubbled through the solution, to yield the thione 8. The thione
- 10 8 is combined with ethyl bromopyruvate and heated to form the thiazolyl carboxylate ester 9. Aqueous LiOH is heated with the ester 9 at a temperature above RT and preferably at reflux to give the thiazole carboxylic acid 10. Treatment of the substituted
- 15 thiazolyl carboxylic acid 10 with base in a suitable solvent at about RT yields a salt. At about  $0^\circ C$ , oxalyl chloride is added to a suspension of the salt in solvent followed by a catalytic amount of DMF. Afterwards, aqueous  $NaN_3$  is added to yield the
- 20 thiazolyl carbonyl azide 11. The carbonyl azide 11 is added to substituted amines to form the thiazolyl urea compound 12.

## Scheme 4



Substituted 4-thiazolylurea compounds 12 are alternatively prepared from the corresponding thiazole acids 10 according to the method set out in Scheme 4. Substituted acids 10 are reacted with diphenylphosphoryl azide in solvent to yield the azido compound 11. The azido compound is hydrolyzed to yield the aniline 13. Acylating agents, such as acid chlorides or anhydrides, are added to the aniline to form the carbamate 14. The carbamates 14 are reacted with substituted amines to form the thiazolyl urea compounds 12.

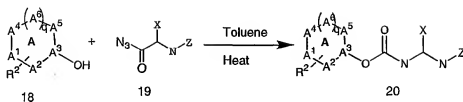
## Scheme 5



- 5 Substituted urea compounds 17 are prepared from the corresponding acids 15 according to the method set out in Scheme 5. Treatment of substituted carboxylic acids 15 with base in a suitable solvent at RT yields the sodium salt. A suspension of the salt in solvent
- 10 is cooled in an ice bath and oxalyl chloride is added followed by a catalytic amount of DMF. Afterwards, aqueous sodium azide is added yielding the carbonyl azides 16. The carbonyl azides 16 are added to substituted amines to form the ureas 17.

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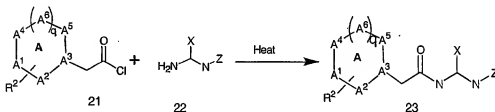
## Scheme 6



Substituted carbamates 20 are prepared from the  
 5 corresponding alcohols 18 and azides 19 according to  
 the method set out in Scheme 6. Treatment of  
 substituted alcohols 18 with azides 19 in a suitable  
 solvent yields the carbamates 20.

10

## Scheme 7

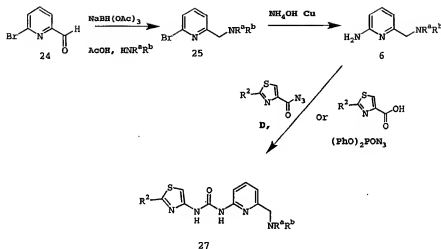


Substituted amides 23 are prepared from the  
 15 corresponding acylating agents 21 (such as acid  
 chlorides or anhydrides) and amines 22 according to the  
 method set out in Scheme 7. Treatment of substituted  
 amines 22 with acylating agents 21 in a suitable  
 solvent yields the amides 23.

20

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## Scheme 8



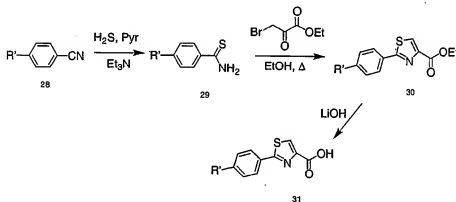
- 5 Substituted 4-thiazolylurea compounds 27 are prepared from the corresponding pyridines 24 according to the method set out in Scheme 8. Reductive amination with an amine (including nitrogen-containing heterocycles) and 6-bromo-2-pyridinecarboxaldehyde 24,
- 10 is achieved such as in a halocarbon solvent such as dichloromethane, in the presence of  $\text{NaBH}(\text{OAc})_3$  and acid, such as  $\text{AcOH}$ , to give 2-aminomethyl-6-bromopyridine 25. The 2-aminomethyl-6-bromopyridine 25 is aminated, such as with  $\text{NH}_4\text{OH}$  in the presence of  $\text{Cu}$
- 15 powder, such as in the presence of an alcohol solvent, at a temperature above about  $50^\circ\text{C}$  and preferably at about  $100^\circ\text{C}$ , such as in a sealed tube to give the corresponding aniline 6. A substituted thiazolylcarbonylurea, such as in dry hydrocarbon
- 20 solvent such as toluene was heated at a temperature above about  $50^\circ\text{C}$  and preferably above about  $85^\circ\text{C}$  and

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reacted with the aniline **6** to give the 4-thiazolylurea compounds **27**.

Alternatively, the aniline **6** can be coupled with thiazolyl carboxylic acid, such as with  $(\text{PhO})_2\text{PON}_3$  in the presence of base, such as TEA, and molecular sieves in a solvent like THF. The reaction can be heated at a temperature above about 50°C and preferably at about reflux yielding the 4-thiazolylurea compounds **27**.

10

**Scheme 9**

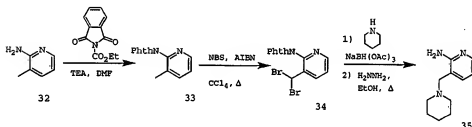
Thiazolyl carboxylic acid **31** (especially appropriate where R' is a sulfonamide or amine) are prepared from the corresponding benzonitriles **28** as described in Scheme 9.  $\text{H}_2\text{S}$  was added to the substituted 4-cyanobenzene **28** in the presence of base, such as  $\text{Et}_3\text{N}$  to afford the thiobenzamide **29**. The thiobenzamide **29** was reacted with ethyl bromopyruvate, such as in an alcohol solvent like  $\text{EtOH}$ , at a temperature greater than about 50°C, and preferably at about 75°C to give the thiazolyl ester **30**. The thiazolyl ester **30** is hydrolyzed, such as with  $\text{LiOH}$

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monohydrate in an alcohol like aqueous MeOH, at a temperature greater than about 50°C, and preferably at about 75°C, to provide the acid **31**. The acid can be used similar to that described in Scheme 8.

5

### Scheme 10



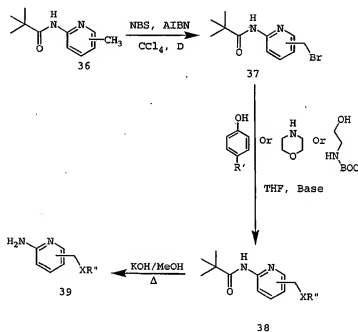
Substituted anilines **35** are prepared from the corresponding methyl compounds **32** as described in Scheme 10. 2-Amino-3-picoline was protected such as with solid carboethoxyphthalimide and base like TEA to provide the phthalimide (Phth) protected aniline **32**. The protected 3-methylaniline is brominated, such as with NBS and 2,2'-azobisisobutyronitrile (AIBN) at a temperature above 50°C and preferably at about reflux. Additional AIBN and NBS may be needed to push the reaction to completeness. The dibromomethyl aniline **34** is reacted with an amine, preferably a secondary amine such as substituted or unsubstituted nitrogen containing heterocyclics like piperidines and piperazines, in the presence of acid like glacial AcOH and halocarbon solvent such as  $\text{CH}_2\text{Cl}_2$ . Treatment with  $\text{NaBH}(\text{OAc})_3$  provided the protected substituted methyl compound which was deprotected, such as by treatment with hydrazine monohydrate at a temperature greater than

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about 50°C, and preferably at reflux to provide the substituted aniline **35**.

### Scheme 11

5



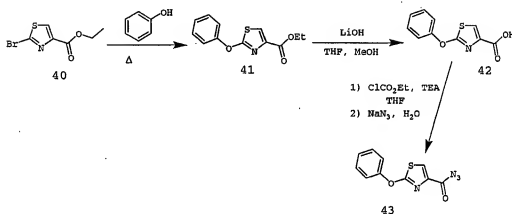
Substituted anilines **39** are prepared from the corresponding methyl compounds **36** as described in Scheme 11. N-Pivaloyl-2-amino-6-bromomethylpyridine **37** was prepared by the method of M.V. Papadopolou, et al. (*J. Heterocyclic Chem.*, 1995, 32, 675-681). The protected bromomethyl compound was treated with an alcohol or amine in the presence of base, such as NaH to yield the corresponding ether or amino alkyl compounds **38** (where X is O or N). The protected ether or amino alkyl compounds **38** was treated with base, such as in methanolic KOH and warmed to a temperature

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greater than about RT, and preferably at about 55°C, to provide the substituted anilines 39.

### Scheme 12

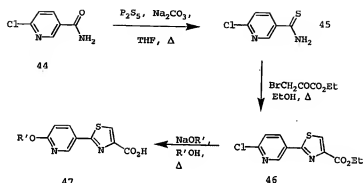
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Thiazolylcarbonylazides 43 are prepared as described in Scheme 12. Bromothiazole was coupled with an aryl alcohol, such as phenol, at a temperature greater than about 100°C, and preferably at about 180°C, to provide the phenoxy compound 41. The thiazolyl ester 41 was hydrolyzed, such as with LiOH monohydrate in an alcohol like aqueous MeOH, at a temperature greater than about 50°C, and preferably at about 75°C, to provide the acid 42. Acid 42 is added to ethyl chloroformate and NaN<sub>3</sub>, in the presence of base such as TEA, to provide the azide 43, which can be used as described in Scheme 8.

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## Scheme 13



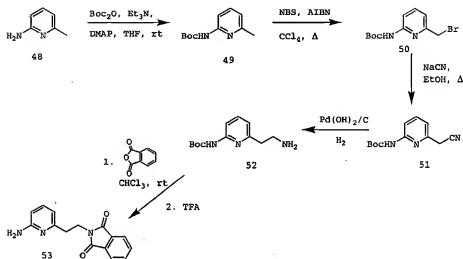
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Pyridyl-2-thiazoles **47** are prepared as described in Scheme 13. 4-Chloronicotinamide **44** was converted to the thioamide **45** such as by treatment with  $P_2S_5$ , in the presence of base, such as  $Na_2CO_3$ , at a temperature greater than about  $50^\circ C$ , and preferably at about reflux. The thioamide **45** is converted to the thiazole ester **46** by treatment with bromoethylpyruvate and heating at a temperature greater than about  $50^\circ C$ , and preferably at about reflux. The ethyl ester is transesterified to the methyl ester with treatment with base, such as NaOMe. Further addition of base and heating at a temperature greater than about  $50^\circ C$ , and preferably at about reflux, hydrolyzed the ester to the acid. Additional NaOMe, in the presence of MeOH, and heating at a temperature greater than about  $50^\circ C$ , and preferably at about reflux, provided the methoxy substituted pyridine compound **47**. Use of other bases and alcohols provide alternative alkoxy substituted compounds.

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## Scheme 14

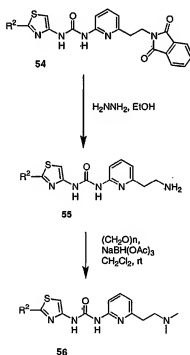


- 5        Protected aminoalkyl pyridines 53 are prepared from the 2-amino-6-methylpyridine 48 as described in Scheme 14. The amino group of 2-amino-6-methylpyridine 48 is protected, such as with BOC and normal coupling chemistry, such as with di-tert-butyl dicarbonate and base, like TEA, and DMAP. The protected compound 49 is
- 10        brominated such as with NBS and AIBN and heating at a temperature greater than about 50°C, and preferably at reflux to provide the bromomethyl derivative 50. The bromomethyl derivative 50 is converted to the
- 15        cyanomethyl compound 51 such as with treatment with NaCN in the presence of alcohol solvent such as EtOH, and heating at a temperature greater than about 50°C, and preferably at reflux. The cyanomethyl compound 51 is hydrogenated to the aminoethyl derivative 52 such as
- 20        with hydrogen in the presence of  $\text{Pd}(\text{OH})_2/\text{C}$  at a temperature about RT. The aminoethyl derivative 52 is

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converted to the di-protected compound such as with phthalic anhydride and heating at a temperature between RT and about 70°C. Upon treatment with strong acid, such as TFA, provides the 2-aminopyridyl compound 53.

5

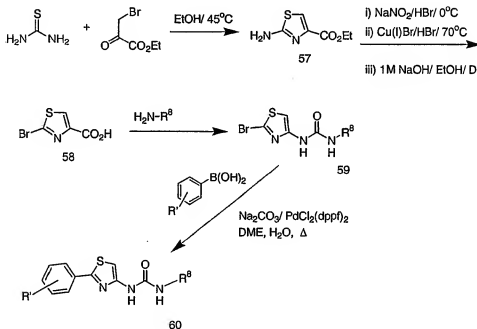
**Scheme 15**

10           Compounds of Formula I are prepared as described  
in Scheme 15. Phthalimidylethyl compounds 54 are  
prepared from the coupling of compounds prepared  
similar to those described in Scheme 14 and thiazolyl  
acylazides as described in Scheme 8. Treatment of 54  
15 with hydrazine hydrate and heating at a temperature  
greater than about 50°C, and preferably at reflux,  
provides the aminoethyl derivatives 55. Alkylation of

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the amine **55**, such as with paraformaldehyde and  $\text{NaBH}(\text{OAc})_3$  in a haloalkyl solvent, such as  $\text{CH}_2\text{Cl}_2$  provides the dimethylamine **56**.

5

**Scheme 16**

Compounds of Formula I (where  $\text{R}^7$  is optionally substituted phenyl) are prepared as described in Scheme 16. The 2-aminothiazole **57** was prepared from thiourea and ethyl bromopyruvate, in an alcoholic solvent like ethanol, at a temperature greater than about RT, and preferably at about  $45^\circ\text{C}$ . Treatment of the ethyl 2-aminothiazole-4-carboxylate with  $\text{HBr}$ ,  $\text{NaNO}_2$ ,  $\text{CuBr}$  and heating at a temperature greater than about  $50^\circ\text{C}$ , and preferably at about  $70^\circ\text{C}$ , provides the bromo thiazole ester. Hydrolysis of the ester, such as with aqueous  $\text{NaOH}$  and alcohol, such as  $\text{EtOH}$  and heating at a

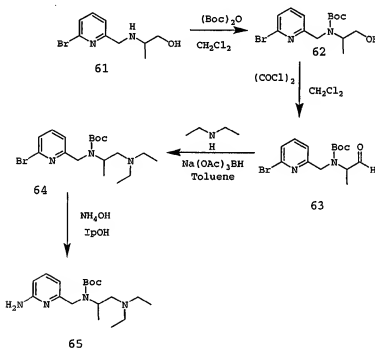
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temperature greater than about 50°C, and preferably at reflux provides the bromothiazole acid **58**. Coupling with substituted amines, similar to that described in Scheme 8, provides the 2-bromothiazolyl urea **59**.

- 5 Suzuki coupling of 2-bromothiazolyl urea **59** with phenyl boronic acids provides the compounds where R<sup>7</sup> is optionally substituted phenyl **60**.

### Scheme 17

10



Substituted aminopyridines **65** are prepared by the method described in Scheme 17. 2-[(6-Bromo-2-pyridyl)methyl]aminopropan-1-ol **61** was protected such as with Boc with di-tert-butylidicarbonate in dry  $\text{CH}_2\text{Cl}_2$ . Conversion to the aldehyde **63** was accomplished by treatment with oxalyl chloride (in  $\text{CH}_2\text{Cl}_2$ ), and DMSO

15

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- at a temperature below about -23°C and preferably at about -63°C, until all the starting material was consumed. Addition of base such as DEA to the aldehyde 63, and heating to reflux in a Dean-Stark trap, followed by the addition of a solution of  $\text{NaBH}(\text{OAc})_3$  in acid such as AcOH at RT provided the aminoalkylaminoalkyl derivative 64. The aminopyridine 65 is prepared as described above.
- The following examples contain detailed descriptions of the methods of preparation of compounds of Formulas I-V. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

The following abbreviations are used:

- |                                 |                   |
|---------------------------------|-------------------|
| RT -                            | RT                |
| 25 H <sub>2</sub> O -           | water             |
| Na <sub>2</sub> SO <sub>4</sub> | sodium sulfate    |
| Na <sub>2</sub> CO <sub>3</sub> | sodium carbonate  |
| Et <sub>2</sub> O -             | diethyl ether     |
| DMSO -                          | dimethylsulfoxide |
| 30 NaOMe                        | sodium methoxide  |
| NaCl -                          | sodium chloride   |

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	MgCl <sub>2</sub> -	magnesium chloride
	EDTA -	ethylenediaminetetraacetic acid
	BSA -	bovine serum albumin
	ATP -	adenosine triphosphate
5	NaN <sub>3</sub> -	sodium azide
	Tris-HCl -	Tris(hydroxymethyl)aminomethane hydrochloride salt
	EGTA -	ethylene glycol-bis(β-aminoethyl ether)- N,N,N', N'-tetraacetic acid
10	DTT -	dithiothreitol
	NaOH -	sodium hydroxide
	mg -	milligram
	g -	gram
	ml -	milliliter
15	EtOAc -	ethyl acetate
	h -	hour
	min -	minutes
	Et <sub>3</sub> N, TEA -	triethylamine
	DEA -	diethylamine
20	KOH -	potassium hydroxide
	THF -	tetrahydrofuran
	LiOH -	lithium hydroxide
	Et <sub>2</sub> NH -	diethylamine
	IpOH -	isopropanol
25	MeOH -	methanol
	EtOH -	ethanol
	CH <sub>3</sub> CN -	acetonitrile
	DMF -	dimethylformamide
	MgSO <sub>4</sub> -	magnesium sulfate
30	NH <sub>4</sub> OH -	ammonium hydroxide
	LiAlH <sub>4</sub> -	lithium aluminum hydride

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	NH <sub>3</sub> -	ammonia
	CH <sub>2</sub> Cl <sub>2</sub> -	dichloromethane
	P <sub>2</sub> S <sub>5</sub> -	phosphorous pentasulfide
	HCl -	hydrochloric acid
5	HBr -	hydrobromic acid
	SOV -	sodium orthovanadate
	MnCl <sub>2</sub> -	manganese chloride
	Cu -	copper
	CuBr -	copper (I) bromide
10	H <sub>2</sub> S -	hydrogen sulfide
	AcOH -	acetic acid
	NaBH(OAc) <sub>3</sub> -	sodium trisacetoxo borohydride
	NaH -	sodium hydride
	TEA -	triethylamine
15	BOC -	tert-butyloxycarbonyl
	DMAP -	4-(dimethylamino)pyridine
	Na <sub>2</sub> HCO <sub>3</sub> -	sodium bicarbonate
	DIEA -	diisopropylethylamine
	EDC -	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
20	AcCN -	acetonitrile
	PtO <sub>2</sub> -	platinum oxide
	TFA -	trifluoroacetic acid
	NaCNBH <sub>3</sub> -	sodium cyanoborohydride
25	NaBH <sub>4</sub> -	sodium borohydride
	HOBt -	hydroxybenzotriazole
	BOP-Cl -	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
	(PhO) <sub>2</sub> PON <sub>3</sub> -	diphenylphosphoryl azide
30	NBS -	N-bromosuccinimide
	Pd(OH) <sub>2</sub> /C -	palladium hydroxide on carbon

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**Procedure A: 2-Amino-6-morpholinopyridine:**

A mixture of 2-chloro-6-aminopyridine (200 mg, 1.49 mmol), morpholine (326 mg, 3.75 mmol) and phenol (2 g) was heated at 150°C for 20 h. After cooling to RT, 3N NaOH (10ml) was added and the mixture was extracted with EtOAc (3x50ml). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude was purified by chromatography on silica gel (1:10 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the morpholino derivative as an amber oil. MS m/z: 180 (M+1).

**Procedure B: 2-Bromo-6-N,N-diethylamidopyridine:**

Ethyl chloroformate (1.76 g, 16.3 mmol) was added dropwise to a mixture of 6-bromopicolinic acid (3 g, 14.8 mmol) and Et<sub>3</sub>N (1.8 g, 17.8 mmol) in THF (150 ml) at 0°C. After the mixture was stirred for 1 h, DEA (1.3 g, 17.8 mmol) was added slowly to the mixture at 0°C. The resulting mixture was stirred at RT for 5 h. H<sub>2</sub>O (200 ml) was added and the mixture was extracted with EtOAc (3x120 ml). The combined organic layers were washed with 1N NaOH and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated *in vacuo* to afford 2-bromo-6-N,N-diethylamidopyridine as an amber oil. MS m/z: 259 (M+1).

**Procedure C: 2-Amino-6-N,N-diethylamidopyridine:**

A mixture of 2-bromo-6-N,N-diethylamidopyridine (3.5 g), 50 ml of 37% NH<sub>4</sub>OH and 0.8 g of Cu powder in 40 ml of IpOH was heated at 100°C in sealed tube for 20 h. After cooling to RT, brine was added and the mixture

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was extracted with EtOAc (3X120 ml). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to afford the amino derivative as a light amber solid. MS m/z:

5 194 (M+1).

**Procedure D: 2-Amino-6-N,N-diethylaminomethylpyridine:**

To a solution of 2-amino-6-N,N-diethylamidopyridine (2.2 g, 11.4 mmol) in 200 ml of

10 THF was added slowly 34.2 ml of  $\text{LiAlH}_4$  (1.3 g, 34.2 mmol) solution in  $\text{Et}_2\text{O}$  at  $0^\circ\text{C}$ . The resulting mixture was heated at reflux for 6 h. After cooling to  $0^\circ\text{C}$ , 2 ml of  $\text{H}_2\text{O}$ , 1.3 ml of 15% NaOH and 7.5 ml of  $\text{H}_2\text{O}$  was added to the mixture sequentially. After stirring for 2

15 h at RT, the mixture was filtered through Celite®. The filtrate was concentrated and purified by chromatography on silica gel (1:10  $\text{MeOH}(\text{NH}_3)/\text{CH}_2\text{Cl}_2$ ) to afford the aminomethyl compound as an amber oil. MS m/z: 180 (M+1).

20

**Procedure E: 2-Amino-6-(N-methylpiperazinyl)pyridine:**

A mixture of 2-bromo-6-aminopyridine (3 g, 17.34 mmol), 1-methylpiperazine (2.3 g, 22.54 mmol) and Cu powder (0.5 g, 7.87 mmol) in 5 ml of 2,4-diethylphenol

25 was heated at  $150^\circ\text{C}$  for 20 h. After cooling to RT, 3N HCl (30 ml) was added and the mixture was extracted with  $\text{Et}_2\text{O}$  (2x100 ml). The aqueous layer was basified with concentrated  $\text{NH}_4\text{OH}$  to  $\text{pH}>10$  and then extracted with EtOAc (3x100 ml). The combined organic layers were

30 washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude was purified by

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chromatography on silica gel (1:10 MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to afford the piperazinyll compound as a light amber solid. MS m/z: 193 (M+1).

5 **Procedure F: 2-Amino-6-(4-morpholino)propylamino-pyridine:**

A mixture of 2-bromo-6-aminopyridine (0.5 g, 2.92 mmol), 4-(3-aminopropyl)morpholine (1.5 g 10.42 mmol) and Cu powder (0.6 g, 9.52 mmol) in 15 ml of IpOH and 5  
10 ml of H<sub>2</sub>O was heated at 100°C in a sealed tube for 24 h. After cooling to RT, water was added and the mixture was extracted with EtOAc (3X50 ml). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude  
15 was purified by chromatography on silica gel (1:10 MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to afford the morpholino compound as an amber oil. MS m/z: 237 (M+1).

20 **Procedure G: 2-Amino-6-(2-N,N-dimethylamino)ethylaminopyridine:**

A mixture of 2-bromo-6-aminopyridine (0.3 g, 1.17 mmol), N,N-dimethylethylenediamine (1 g, 11.36 mmol) and Cu powder (0.74 g, 11.7 mmol) in 30 ml of IpOH was heated at 100°C in seal tube for 20 h. After cooling to  
25 RT, water was added and the mixture was extracted with EtOAc (3x50 ml). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude was purified by chromatography on silica gel (1:10 MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to  
30 afford the aminoethyl compound as an oil. MS m/z: 181 (M+1).

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**Procedure H: Amino-2-pyridylmethane-1-thione:**

2-Cyanopyridine (2.6 g, 0.025 mol) was added to a solution of TEA (5.5 ml) and dry pyridine (50 ml) at  
5 RT. H<sub>2</sub>S was bubbled through the solution for 1 h. Afterwards, H<sub>2</sub>O (150 ml) was added and the mixture was extracted with EtOAc (3x50ml). The EtOAc extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under vacuum. The resulting residue was  
10 purified by column chromatography eluting with hexanes:EtOAc (4:1) to give amino-2-pyridylmethane-1-thione as a light yellow solid. GC/MS m/z: 139 (M+H); GC Retention time: 7.93 minutes.

**Procedure I: 2-(2-Pyridinyl)thiazole-4-carboxylic acid:**

Amino-2-pyridylmethane-1-thione (1.88 g, 0.0136 mol), ethyl bromopyruvate (1.80 ml, 0.0143 mol) and EtOH (30 ml) were combined and heated to reflux. GC/MS  
of reaction mixture after 3 h showed total consumption  
15 of the starting materials. After cooling to RT, the solvent was removed under vacuum resulting in a dark brown oil (GC/MS m/z: 235 (M+H); GC Retention time: 10.69 minutes). The material was taken up in MeOH (20 ml), 1.0M LiOH-H<sub>2</sub>O (20 ml) was added and the mixture  
20 was heated to 100°C for 14 h. After cooling to RT, the excess MeOH was evaporated and the resulting brown solid filtered. The material was washed with a minimum of H<sub>2</sub>O and dried *in vacuo* to give the thiazole as a  
25 brown solid.

30

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**Procedure J: 2-(4-Pyridinyl)-4-thiazolylcarbonylazide:**

To a suspension of 2-(4-pyridinyl)-4-thiazolylcarboxylic acid (Maybridge Chem., 6.0 g, 29.1 mmol) in 150 ml MeOH at RT was added NaOH (1.28 g, 32.0 mmol) and the mixture was stirred at RT for 45 min. The reaction mixture was concentrated *in vacuo* then dried under high vacuum for 60 h (overnight drying is a minimum). The crude salt was suspended in 150 ml of CH<sub>2</sub>Cl<sub>2</sub> and cooled in an ice bath. Oxalyl chloride (2.8 ml) was added slowly to the suspension followed by a catalytic amount of DMF (0.2 ml). The mixture was stirred for 2 h and warmed to RT. The reaction was cooled in an ice bath and a solution of NaN<sub>3</sub> (2.27 g) in water (90 mL) was added and stirring was continued for 3 h. The reaction mixture was diluted with water (90 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x75ml). The combined organic layers were filtered through Celite® (~12 g) washed with 90 mL brine, dried with MgSO<sub>4</sub> and concentrated *in vacuo*. Drying the crude compound on the vacuum line afforded the azido derivative as a light brown solid. MS *m/z*: 204.5 (M-N<sub>2</sub>+H).

**Procedure K: 2-(3-Pyridinyl)-4-thiazolylcarbonylazide:**

In a manner similar to that described for the preparation of 2-(4-pyridinyl)-4-thiazolylcarbonylazide, 6.0 g of 2-(3-pyridinyl)-4-thiazolylcarboxylic acid was treated successively with NaOH, oxalyl chloride and a solution of NaN<sub>3</sub> in water to give the 3-pyridinylazide as a pale brown solid. MS *m/z*: 204.5 (M-N<sub>2</sub>+H).

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**Procedure L: 2-(2-Pyridinyl)-4-thiazolylcarbonylazide:**

In a manner similar to that described for the preparation of 2-(4-pyridinyl)-4-thiazolylcarbonylazide, 2-(2-pyridinyl)-4-thiazolylcarboxylic acid (1.0 g) was treated successively with NaOH, oxalyl chloride and a solution of  $\text{NaN}_3$  in water to give the 2-pyridinyl azide as a pale brown solid: m.p. 112-114°C. MS m/z: 232 (M+H).

**Procedure M: 2-Phenyl-4-thiazolylcarbonylazide:**

In a manner similar to that described for the preparation of 2-(4-pyridinyl)-4-thiazolylcarbonylazide, 1.0 g of 2-phenyl-4-thiazolylcarboxylic acid was treated successively with NaOH, oxalyl chloride and a solution of  $\text{NaN}_3$  in water to give the phenylazide as an off white solid. MS m/z: 203.5 (M- $\text{N}_2$ +H).

**Procedure N: 4-(6-Bromo-pyridin-2-ylmethyl)-morpholine**

To a stirred solution of 6-bromo-2-pyridinecarboxaldehyde (200 mg, 1.08 mmol) in dichloroethane (10 mL) was added morpholine (0.14 mL, 1.62 mmol) followed by  $\text{NaBH}(\text{OAc})_3$  (458 mg, 2.16 mmol) and AcOH (0.25 mL, 4.32 mmol). The resulting mixture was stirred at RT for 12 h. The reaction was quenched with 2M  $\text{Na}_2\text{CO}_3$  solution and stirred 1 h. The mixture was poured into  $\text{Et}_2\text{O}$  and washed with 2 M  $\text{Na}_2\text{CO}_3$  solution. The organic layer was collected, dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo to give 2-bromo-6-morpholinylmethylpyridine as a white solid. MS m/z: 256.9 (M+H).

30

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The following compounds were prepared in a manner similar to that described above:

- 1] 1-(6-Bromopyridin-2-ylmethyl)-piperidine-4-carboxylic acid ethyl ester, as a pale yellow solid, was prepared in a manner similar to that described in General Procedure N [6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.16 mmol) was added to ethyl isonipecotate (0.5 mL, 3.24 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL)]. MS m/z: 327.0 (M+H). Calc'd for  $\text{C}_{14}\text{H}_{19}\text{BrN}_2\text{O}_2$ : 326.90.
- 2] To 6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.16 mmol) was added L-leucinol (0.42 mL, 3.24 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) to give 2-[(6-bromo-pyridin-2-ylmethyl)-amino]-4-methyl-pentan-1-ol as brown solid. MS m/z: 287.6 (M+H). Calc'd for  $\text{C}_{12}\text{H}_{19}\text{BrN}_2\text{O}$ : 287.2.
- 3] To 6-bromo-2-pyridinecarboxaldehyde (500 mg, 2.69 mmol) was added 1,4-dioxo-8-azaspiro-[4,5]-decane (0.5 mL, 4.03 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) to give 2-bromo-6-(4-ethoxyacetal)-piperidinylmethylpyridine as white solid. MS m/z: 313 (M+H). Calc'd for  $\text{C}_{13}\text{H}_{17}\text{BrN}_2\text{O}_2$ : 313.2.
- 4] To 6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.15 mmol) was added 3,5-dimethylpiperidine (0.4 mL, 3.22 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) to give 2-bromo-6-(3,5-dimethyl)piperidinylmethyl

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pyridine as white solid. MS m/z: 283.2 (M+H).  
Calc'd for  $C_{13}H_{19}BrN_2$ : 283.2

- 5] To 6-bromo-2-pyridinecarboxaldehyde (400 mg,  
2.15 mmol) was added 4-methylpiperidine (0.4  
mL, 3.22 mmol) in dry  $CH_2Cl_2$  (10 mL) to give 2-  
bromo-6-[(4-methyl)piperidinylmethyl]pyridine  
as a white solid. MS m/z: 269.4 (M+H). Calc'd  
for  $C_{12}H_{17}BrN_2$ : 269.18.
- 6] To 6-bromo-2-pyridinecarboxaldehyde (400 mg,  
2.15 mmol) was added 2-methylpiperidine (0.4  
mL, 3.22 mmol) in dry  $CH_2Cl_2$  (10 mL) to give 2-  
bromo-6-[(2-methylpiperidinyl)methyl]pyridine  
as a pale yellow solid. MS m/z: 269.1 (M+H).  
Calc'd for  $C_{12}H_{17}BrN_2$ : 269.18.
- 7] To 6-bromo-2-pyridinecarboxaldehyde (400 mg,  
2.15 mmol) was added 4-(1-pyrrolidinyl)-  
piperidine (500 mg, 3.22 mmol) in dry  $CH_2Cl_2$  (15  
mL) to give 2-bromo-6-[4-(1-pyrrolidinyl)-  
piperidinylmethyl]pyridine as a pale yellow  
solid. MS m/z: 326.1 (M+2H). Calc'd for  
 $C_{15}H_{22}BrN_3$ : 324.26.
- 8] To 6-bromo-2-pyridinecarboxaldehyde (400 mg,  
2.15 mmol) was added 3-hydroxypiperidine (326  
mg, 3.22 mmol) in dry  $CH_2Cl_2$  (15 mL) to give 2-  
bromo-6-(3-hydroxypiperidinyl)methyl pyridine  
as pale yellow solid. MS m/z: 271.2 (M+H).  
Calc'd for  $C_{11}H_{15}BrN_2O$ : 271.15.

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- 9] To 6-bromo-2-pyridinecarboxaldehyde (300 mg, 1.62 mmol) was added hexamethyleneimine (0.27 mL, 2.43 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) to give 2-bromo-6-(azaperhydroepinylmethyl)pyridine as a white solid. MS m/z: 270.3 (M+H). Calc'd for  $\text{C}_{12}\text{H}_{17}\text{BrN}_2$ : 269.18.
- 10] To 4-hydroxypiperidine (143 mg, 1.41 mmol) was added a solution of 6-bromo-2-pyridine-carboxaldehyde (200 mg, 1.08 mmol) to give 2-bromo-6-[(4-hydroxypiperidyl)methyl]-pyridine as a white solid. MS m/z: 271.0 (M+H). Calc'd for  $\text{C}_{11}\text{H}_{15}\text{BrN}_2\text{O}$  - 271.15.
- 11] 3-Hydroxypropylamine (0.15 mL, 2.02 mmol) was added to a solution of 6-bromo-2-pyridine-carboxaldehyde (250 mg, 1.35 mmol) to give 2-bromo-6-[(3-hydroxypropyl)amino]-methylpyridine as a white solid. MS m/z: 245.1 (M+H). Calc'd for  $\text{C}_{11}\text{H}_{13}\text{BrN}_2\text{O}$  - 245.19.
- 12] Ethyl(piperidyl-3-carboxylate (0.92 mL, 5.92 mmol) was added to a solution of 6-bromo-2-pyridinecarboxaldehyde (1.0 g, 5.38 mmol) to give ethyl 1-[(6-bromopyridin-2-yl)methyl]-piperidine-3-carboxylate as a colorless oil. MS m/z: 327.1 (M+H). Calc'd for  $\text{C}_{14}\text{H}_{19}\text{BrN}_2\text{O}_2$  - 327.22.

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- 13] Ethyl (2-piperidyl)carboxylate (0.92 mL, 5.92 mmol) was added to a solution of 6-bromo-2-pyridinecarboxaldehyde (1.0 g, 5.38 mmol) to give ethyl 1-[(6-bromopyridin-2-yl)methyl]-piperidine-2-carboxylate as a colorless oil). MS  $m/z$ : 327.1 (M+H). Calc'd for  $C_{14}H_{19}BrN_2O_2$  - 327.22.
- 14] N,N-Diethylcarbamoyl-piperidine-3-carboxamide (0.92 mL, 5.92 mmol) was added to a solution of 6-bromo-2-pyridinecarboxaldehyde (1.0 g, 5.38 mmol) to give N,N-diethyl 1-(6-bromopyridin-2-ylmethyl)piperidine-3-carboxamide as a colorless oil. MS  $m/z$ : 354.1 (M+H). Calc'd for  $C_{16}H_{24}BrN_3O$  - 354.29.
- 15] 2-Pyrrolidine carboxylic acid (0.68 g, 5.92 mmol) was added to a solution of 6-bromo-2-pyridine-carboxaldehyde (1.0 g, 5.38 mmol) to give 1-(6-bromopyridin-2-ylmethyl)-pyrrolidine-2-carboxylic acid as a white solid. MS  $m/z$ : 285.1 (M+H). Calc'd for  $C_{11}H_{13}BrN_2O_2$  - 285.14.
- 16] 3-Methylpiperidine (0.33 mL, 2.8 mmol) was added to a solution of 6-bromo-2-pyridine-carboxaldehyde (350 mg, 1.88 mmol) to give 2-bromo-6-[(3-methylpiperidyl)methyl]pyridine as a white solid. MS  $m/z$ : 269.1 (M+H). Calc'd for  $C_{12}H_{17}BrN_2$  - 269.18.

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**Procedure O: 6-Morpholin-4-ylmethyl-pyridin-2-ylamine**

NH<sub>4</sub>OH (2 mL) and Cu powder (10 mg, 0.15 mmol) were added to a solution of 2-bromo-6-morpholinylpyridine (231 mg, 0.90 mmol) in IpOH (5 mL) and the resulting  
5 mixture was heated at 100°C for 36 h in a sealed tube. After cooling to RT, the mixture was partitioned between H<sub>2</sub>O and EtOAc. The organic layer was collected, washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo gave the tilted compound as a  
10 pale yellow solid. MS m/z: 194.1 (M+H).

The following amines were prepared from the corresponding bromo compounds (prepared by Procedure N) in a manner similar to that described in General

15 Procedure O:

- 1] 1-(6-amino-pyridin-2-ylmethyl)-piperidine-4-carboxylic acid ethyl ester as brown liquid. MS  
20 m/z: 264.2 (M+H). Calc'd for C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: 263.34.
- 2] 2-amino-6-[N'-tert-butoxycarbonyl-N'-2-(1-hydroxy-4-methyl)pentylamino]methylpyridine as a brown liquid. MS m/z: 324.3 (M+H). Calc'd  
for C<sub>17</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>: 323.2.
- 25 3] 2-amino-6-(4-ethoxyacetalpiperidinyl)-methylpyridine as a white solid. MS m/z: 250 (M+2H). Calc'd for C<sub>13</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>: 249.1.

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- 4] 2-Amino-6-(3,5-dimethylpiperidinyl)methylpyridine as a yellow solid. MS m/z: 220.3 (M+H). Calc'd for  $C_{13}H_{21}N_3$ : 219.
- 5] 2-Amino-6-(4-methylpiperidinyl)methylpyridine as a yellow solid. MS m/z: 206.3 (M+H). Calc'd for  $C_{12}H_{19}N_3$ : 205.28.
- 6] 2-Amino-6-(2-methylpiperidinyl)methylpyridine as a yellow liquid. MS m/z: 206.3 (M+H). Calc'd for  $C_{12}H_{19}N_3$ : 205.28.
- 7] 2-Amino-6-[[4-(1-pyrrolidinyl)piperidinyl)methyl]-pyridine as a brown liquid (335 mg, 93%). MS m/z: 261.1 (M+2H). Calc'd for  $C_{12}H_{19}N_3$ : 260.
- 8] 2-Amino-6-(3-hydroxypiperidinyl)methylpyridine as a yellow liquid. MS m/z: 410.9 (M+H). Calc'd for  $C_{11}H_{17}N_3O$ : 410.5.
- 9] 2-Amino-6-(azaperhydroepinylmethyl)pyridine as a white solid. MS m/z: 206.1 (M+H). Calc'd for  $C_{12}H_{19}N_3$ : 205.32.
- 10] 2-Amino-6-[(4-hydroxypiperidyl)methyl]pyridine as a pale yellow oil. MS m/z: 208.1 (M+H). Calc'd for  $C_{11}H_{17}N_3O$ : 207.27.
- 11] 2-Amino-6-[(N-tert-butoxycarbonyl-N-(3-hydroxypropyl)amino)methyl]pyridine as a pale

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yellow oil. MS  $m/z$ : 282.3 (M+H). Calc'd for  $C_{14}H_{23}N_3O_3$  - 281.35.

5 12] Ethyl 1-[(6-aminopyridin-2-yl)methyl]-  
piperidine-3-carboxylate as a pale yellow oil.  
MS  $m/z$ : 264.1 (M+H). Calc'd for  $C_{14}H_{21}N_3O_2$  -  
263.34.

10 13] Ethyl 1-[(6-aminopyridin-2-yl)methyl]-  
piperidine-2-carboxylate as a pale yellow oil.  
MS  $m/z$ : 264.1 (M+H). Calc'd for  $C_{14}H_{21}N_3O_2$  -  
263.34.

15 14] N,N-Diethyl 1-(6-aminopyridin-2-ylmethyl)-  
piperidine-3-carboxamide as a pale yellow oil.  
MS  $m/z$ : 291.5 (M+H). Calc'd for  $C_{16}H_{26}N_4O$  -  
290.40.

20 15] 1-(6-Aminopyridin-2-ylmethyl)-pyrrolidine-2-  
carboxylic acid as a white solid. MS  $m/z$ :  
220.3 (M-H). Calc'd for  $C_{11}H_{15}N_3O_2$  -221.26.

25 16] 2-Amino-6-[(3-methylpiperidyl)methyl]pyridine  
as a pale yellow solid (250 mg, 68%). MS  $m/z$ :  
206.5 (M+H). Calc'd for  $C_{12}H_{19}N_3$  - 205.30.

30 17] 1-(6-Aminopyridin-2-ylmethyl)-piperidine-3-  
carboxylic acid as a pale yellow oil. MS  $m/z$ :  
235.0 (M+H). Calc'd for  $C_{12}H_{17}N_3O_2$  -235.28.

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Procedure P: 4-(6-Aminopyridin-2-yloxy)-benzonitrile

To a stirred solution of 4-cyanophenol (1.7 g, 14.3 mmol) in 45 mL dry DMF was added NaH (0.71 g, 17.7 mmol). After stirring at RT for 15 min, 2,6-dibromopyridine (3.2 g, 13.4 mmol) was added and the mixture was heated at 95°C for 24 h. After cooling to RT, 100 mL of H<sub>2</sub>O was added and the mixture was extracted with EtOAc (2x100 mL). The combined organic layers were washed with 40 mL brine, dried over MgSO<sub>4</sub> and concentrated in vacuo. The crude intermediate was dissolved in 20mL IpOH, transferred to a Teflon lined pressure vessel and 20 mL of conc. NH<sub>4</sub>OH was added. Powdered Cu (1 g) was added and the vessel was sealed and heated at 140°C for 24 h. After cooling to RT, the Cu was removed by filtration and the filtrate was diluted with 75 mL of H<sub>2</sub>O and extracted with EtOAc (2x75 mL). The organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated in vacuo. The compound was purified by chromatography on silica gel using 10:1 CHCl<sub>3</sub>/(-2M NH<sub>3</sub>/MeOH) as eluent to afford the title compound (1.5 g, 55 %) as a dark oil. MS m/z: 212.2 (M+H).

The following compounds were prepared from 2,6-dibromopyridine in a manner similar to that described in General Procedure P:

1) 6-Phenoxy-pyridin-2-ylamine: MS m/z: 187.2 (M+H).  
Calc'd for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O: 186.08.

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- 2] 6-(4-Methylphenoxy)pyridin-2-ylamine: MS m/z:  
201.3 (M+H). Calc'd for  $C_{12}H_{12}N_2O$ : 200.09.
- 3] 6-(2,4-Dimethylphenoxy)pyridin-2-ylamine: MS  
5 m/z: 215.3 (M+H). Calc'd for  $C_{13}H_{14}N_2O$ : 214.11.
- 4] 6-[4-(1-Imidazolyl)phenoxy]pyridin-2-ylamine: MS  
m/z: 253.3 (M+H). Calc'd for  $C_{14}H_{12}N_4O$ : 252.10.
- 10 5] 6-[4-[1,3]Dioxolan-2-yl-phenoxy]pyridin-2-ylamine:  
MS m/z: 259.3 (M+H). Calc'd for  $C_{14}H_{14}N_2O_3$ : 258.10.
- 6] 6-(4-Fluorophenoxy)pyridin-2-ylamine: MS m/z:  
205.2 (M+H). Calc'd for  $C_{11}H_9FN_2O$ : 204.07.
- 15 7] 6-(4-Difluorophenoxy)pyridin-2-ylamine: MS m/z:  
223.2 (M+H). Calc'd for  $C_{11}H_8F_2N_2O$ : 222.06.
- 8] tert-Butyl {2-[4-(6-aminopyridin-2-  
20 yloxy)phenyl]ethyl}carbamate: MS m/z: 330.4 (M+H).  
Calc'd for  $C_{18}H_{23}N_3O_3$ : 329.17.
- 9] 6-(2-Dimethylaminoethoxy)pyridin-2-ylamine: MS  
m/z: 182.2 (M+H). Calc'd for  $C_9H_{15}N_3O$ : 181.12.
- 25 10] 6-[(1-Methylpyrrolidin-2-yl)methoxy]pyridin-2-  
ylamine: MS m/z: 208.3 (M+H). Calc'd for  
 $C_{11}H_{17}N_3O$ : 207.14.

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- 11] 6-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)pyridin-2-ylamine: MS m/z: 220.3 (M+H). Calc'd for  $C_{12}H_{17}N_3O$ : 219.14.
- 5 12] tert-Butyl 3-[(6-aminopyridin-2-yl)oxymethyl]-azetidine-1-carboxylate: MS m/z: 280 (M+H). Calc'd for  $C_{14}H_{21}N_3O_3$ : 279.16.
- 13] tert-Butyl 4-[2-(6-Aminopyridin-2-yloxy)ethyl]-piperidine-1-carboxylate: MS m/z: 322 (M+H).  
10 Calc'd for  $C_{17}H_{27}N_3O_3$ : 321.21.

**Preparation Q: 2-Bromo-6-[N'-tert-butoxycarbonyl-N'-2-(1-hydroxy-4-methyl)pentylamino]methylpyridine**

- 15 To 2-bromo-6-[2-N-(1-hydroxy-4-methyl)-pentylamino]methylpyridine (550 mg, 1.91 mmol) in dry  $CH_2Cl_2$  (10 mL) was added  $(Boc)_2O$  (460 mg, 2.106 mmol). The resulting mixture was stirred under  $N_2$  at RT for 15 h. The solvent was removed and the residue was  
20 extracted with  $CHCl_3$ . The organic layer was wash with  $H_2O$ , brine, and dried over  $MgSO_4$  and removed to give a yellow liquid. MS m/z: 387.6(M+H). Calc'd for  $C_{17}H_{27}BrN_2O_3$ : 387.32.

- 25 The following BOC protected compounds were prepared from the corresponding amines (prepared by Procedure N) in a manner similar to that described in General Procedure Q:

- 30 1] 2-Bromo-6-[(N-tert-butoxycarbonyl-N-(3-hydroxypropyl)amino)methylpyridine was prepared

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from 2-bromo-6-[(3-hydroxypropyl)-amino]-  
methylpyridine (300 mg, 1.22 mmol) [purified by  
chromatography on silica gel (hexane/acetone,  
80/20)] as a colorless oil. MS  $m/z$ : 345.1  
5 (M+H). Calc'd for  $C_{14}H_{21}BrN_2O_3$  - 345.23.

**Preparation R: 2,2-Dimethyl-N-[6-(2-methylimidazol-1-  
ylmethyl)pyridin-2-yl]propionamide**

A solution of 2-methylimidazole (68 mg, 0.83 mmol)  
10 in dry THF (8 mL) was treated under  $N_2$  with NaH (33 mg,  
0.83 mmol, 60% in mineral oil) at 0°C. After the  
addition, the mixture was warmed to RT and stirred for  
0.5 h. It was then treated dropwise with a solution of  
N-pivaloyl-2-amino-6-bromomethylpyridine (150 mg, 0.55  
15 mmol; M.V. Papadopolou, et al., *J. Heterocyclic Chem.*,  
1995, 32, 675-681) in dry THF (10 mL) over period of 15  
min. After the addition, it was stirred for 1 h. The  
resulting mixture was quenched with saturated  $NH_4Cl$  (3  
mL). Solvent was removed and the residue was extracted  
20 with  $CHCl_3$ . The organic layer was washed with  $H_2O$ ,  
brine, dried over  $MgSO_4$ , and concentrated in vacuo to  
yield the title compound as light brownish solid (145  
mg, 96%). MS  $m/z$ : 272.2 (M+H). Calc'd. for  $C_{16}H_{21}N_3O$  -  
271.37.

25

The following amines were prepared from the  
corresponding bromomethylpyridine in a manner similar  
to that described in Preparation R:

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1] 2,2-Dimethyl-N-[6-(4-(N,N-dimethylamino-methyl)phenoxy)methyl]pyridin-2-yl]propionamide. MS *m/z*: 342 (M+H).

5 **Preparation S: N-(6-Azidomethylpyridin-2-yl)-2,2-dimethylpropionamide**

*N*-Pivaloyl-2-amino-6-bromomethylpyridine (1.1 g, 4.05 mmol; M.V. Papadopolou, et al., *J. Heterocyclic Chem.*, 1995, 32, 675-681) was dissolved in dry THF (15  
10 mL). NaN<sub>3</sub> (530 mg, 8.1 mmol) and dry DMF (5 mL) was added and the resulting mixture was heated to reflux under N<sub>2</sub> for 2 h. After cooling to RT, solvent was removed and the residue was partitioned between H<sub>2</sub>O and CHCl<sub>3</sub>. The organic layer was washed with H<sub>2</sub>O, brine,  
15 dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give the title compound as a pale yellow solid. MS *m/z*: 234.1 (M+H). Calc'd. for C<sub>11</sub>H<sub>15</sub>N<sub>5</sub>O - 233.28.

**Preparation T: 6-Azidomethyl-pyridin-2-ylamine**

20 2-(*N'*-Pivaloyl)amino-6-azidomethylpyridine (680 mg, 2.91 mmol) was dissolved in MeOH (20 mL) and KOH was added (3.4 g, 60.6 mmol). The resulting mixture was heated to reflux under N<sub>2</sub> for 2 h. After cooling to RT, pH was adjusted to 7 followed by removing the  
25 solvent. The residue was partitioned between H<sub>2</sub>O and CHCl<sub>3</sub> and the aqueous layer was extracted more with CHCl<sub>3</sub>. The combined organic layers was washed with H<sub>2</sub>O, brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to yield the title compound as brown solid. MS *m/z*:  
30 150.3 (M+H). Calc'd. for C<sub>6</sub>H<sub>7</sub>N<sub>5</sub>: 149.15.

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The following amines were prepared from the corresponding bromo compounds (prepared by Preparations R-S, and AA) in a manner similar to that described in Preparation T:

- 5
- 1] 3-(2-Methylimidazol-1-ylmethyl)phenylamine. MS  
m/z: 189.3 (M+H). Calc'd. for  $C_{10}H_{12}N_4$  - 188.23.
- 10
- 2] 2-Amino-6-[4-(dimethylamino)methyl]phenoxyethyl-pyridine.  
MS m/z: 258 (M+H).
- 15
- 3] 2-Amino-6-[1-(N-tert-butoxycarbonyl)amino]-ethoxymethyl-pyridine. MS m/z: 268 (M+H).
- 20
- 4] 2-Amino-6-[4-(methylphenyl)oxymethyl]pyridine.  
MS m/z: 215 (M+H).
- 25
- 5] 2-Amino-6-[1-(N-tert-butoxycarbonyl)amino]-ethoxymethyl-pyridine. MS m/z: 267 (M+H)
- 6] 2-Amino-5-[1-morpholinylmethyl]pyridine. MS  
m/z: 194 (M+H).
- 7] 5-Methoxymethyl-pyridin-2-ylamine.

Preparation U: Methyl 1-(6-aminopyridin-2-ylmethyl)-pyrrolidine-2-carboxylate

- 30
- Concentrated sulfuric acid (1.0 mL) was added to a solution of 1-(6-aminopyridin-2-ylmethyl)-pyrrolidine-2-carboxylic acid (620 mg, 2.80 mmol) in MeOH (15 mL)

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and the resulting mixture was heated at 80°C for 10 h. After cooling to RT, the mixture was quenched with saturated 2 M Na<sub>2</sub>CO<sub>3</sub> solution and concentrated in vacuo. CHCl<sub>3</sub> (15 mL) was added and the solution washed with 1.0 N NaOH solution (15 mL). The organics were collected and the aqueous layer was extracted with CHCl<sub>3</sub>/IpOH (3/1, 3x10 mL). The combined organics were dried over MgSO<sub>4</sub> and concentrated in vacuo. The crude compound was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95/5) to give a pale yellow oil. MS m/z: 236.1 (M+H). Calc'd for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> -235.28.

**Preparation V: 3-Methyl-2-(phthalimidyl)pyridine**

2-Amino-3-picoline (1.00 mL, 8.62 mmol) was dissolved in DMF (30 mL) at 23°C, and treated with solid carboethoxy-phthalimide (1.89 g, 8.64 mmol), followed by TEA (1.44 mL, 10.3 mmol). The resulting solution was stirred at 23°C for 15 h. After 15 h, the mixture was diluted with EtOAc (50 mL), and washed with saturated NaCl (1x50 mL), H<sub>2</sub>O (1x50 mL), dried (MgSO<sub>4</sub>), and concentrated in vacuo to a yellow solid. Purification over silica gel (0 to 50% EtOAc/Hexanes) provided the title compound as a white solid.

**Preparation W: 3-(Dibromomethyl)-2-(phthalimidyl)pyridine**

3-Methyl-2-(phthalimidyl)pyridine (360 mg, 1.51 mmol) was dissolved in CCl<sub>4</sub> (5 mL), and treated with NBS (267 mg, 1.50 mmol), followed by 2,2'-azobisisobutyronitrile (AIBN) (46.9 mg, 0.29 mmol). The resulting suspension was warmed to reflux for 2 h,

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treated again with AIBN (55.4 mg, 0.34 mmol), and heated at reflux an additional 12 h. After 12 h, AIBN was again added (96.7 mg, 0.59 mmol) and reflux was continued. After 2 h, more AIBN was added (59.6 mg, 0.36 mmol), and reflux continued. After 2h, additional NBS was added (253 mg, 1.42 mmol) and the mixture was treated with additional AIBN (49.6 mg, 0.30 mmol), and heated at reflux an additional 12 h. The mixture was cooled to RT, diluted with EtOAc (50 mL), washed with saturated NaCl (1X50 mL), then dried (MgSO<sub>4</sub>) and concentrated in vacuo. The resulting white solid was purified over silica gel (0 to 40% EtOAc/Hexanes) to provide the title compound. MS m/z: 397 (M+H).

15 **Preparation X: 2-(phthalimidyl)-3-(1-piperidinylmethyl)-pyridine**

3-(Dibromomethyl)-2-(phthalimidyl)pyridine (185 mg, 0.47 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and treated with piperidine (.460 mL, 4.66 mmol), and glacial AcOH (.160 mL, 2.80 mmol) in a dropwise fashion. The resulting yellow solution was stirred at 23°C for 2 h, then treated with solid NaBH(OAc)<sub>3</sub> (393 mg, 1.86 mmol) in one portion, and stirring was continued for 14 h. After stirring 14 h at 23°C, the mixture was treated with 2M K<sub>2</sub>CO<sub>3</sub> (6 mL), and stirred for 1 h. After 1 h, the mixture was diluted with EtOAc (50 mL) and washed with H<sub>2</sub>O (1X50 mL), and saturated NaCl (1X50 mL). The organic phase was then dried (MgSO<sub>4</sub>) and concentrated in vacuo to provide the title compound as a yellow residue. The crude material was

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used in subsequent transformations without further purification. MS  $m/z$ : 323 (M+H).

**Preparation Y: 2-Amino-3-(1-piperidinylmethyl)-pyridine**

5        2-(Phthalimidyl)-3-(1-piperidinylmethyl)-pyridine  
(196 mg, 0.609 mmol) was dissolved in EtOH (95%, 2 mL)  
at 23°C, and treated with hydrazine monohydrate (0.0320  
mL, 0.670 mmol) in a dropwise fashion. The resulting  
mixture was warmed to reflux and stirred for 3 h at  
10 reflux. The solution was treated with additional  
hydrazine monohydrate (0.150 mL, 3.050 mmol), and  
reflux continued. After 14 h at reflux, the mixture  
was cooled to RT, and concentrated using a rotary  
evaporator to a white paste. The resulting white paste  
15 was dissolved in  $\text{CHCl}_3$ :iPrOH (3:1, 75 mL), and washed  
with saturated  $\text{NaHCO}_3$  (3X50 mL), and  $\text{H}_2\text{O}$  (1X50 mL).  
The organic layer was dried over  $\text{MgSO}_4$  and concentrated  
in vacuo to provide the title compound as a white  
solid. MS  $m/z$ : 192 (M+H).

20

**Preparation Z: N-Pivaloyl 2-amino-5-(bromomethyl)  
pyridine**

N-Pivaloyl-2-amino-5-methylpyridine (5.12 g, 26.6  
mmol) was dissolved in  $\text{CCl}_4$  (75 mL) at 23°C, and  
25 treated with NBS (9.69 g, 54.4 mmol), followed by 2,2'-  
azobisisobutyronitrile (AIBN) (937 mg, 5.71 mmol) with  
stirring. The resulting orange, biphasic suspension  
was then warmed to reflux for 4h. After 4 h at reflux,  
the rust-colored mixture was cooled to RT, filtered  
30 through a Celite® pad, and concentrated in vacuo to a  
red residue. Purification over silica gel (gradient, 0

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to 25% EtOAc/hexanes) provided the title compound as a light yellow solid. MS  $m/z$ : 272 (M+H).

**Preparation AA: N-Pivaloyl-2-amino-5-[2-(N-tert-butoxycarbonyl)amino]ethoxymethylpyridine**

5 N-Pivaloyl-2-amino-5-bromomethylpyridine (484 mg, 1.78 mmol) was dissolved in THF (6 mL) at 23°C, and treated with 2-(N-tert-butoxycarbonyl)aminoethanol (0.551 mL, 3.56 mmol), followed by NaH (60% suspension 10 in mineral oil, 221 mg, 5.52 mmol) with stirring. The resulting mixture was stirred at 23°C for 14 h, then treated with additional NaH (75.6 mg, 1.89 mmol) as well as DMSO (1 mL), and stirred an additional 5 h at 23°C. After 5 h at 23°C, the solution was warmed to 15 55°C for 3 h, and then cooled to RT. The mixture was treated with saturated NaHCO<sub>3</sub> (10 mL), diluted with EtOAc (50 mL), and washed with saturated NaHCO<sub>3</sub> (2X50 mL). The mixture was dried over MgSO<sub>4</sub> and purified over silica gel to provide the title compound as a pale 20 yellow oil. MS  $m/z$ : 352 (M+H).

The following amines were prepared from the corresponding bromomethylpyridine in a manner similar to that described in General Procedure AA:

25

1] 2,2-Dimethyl-N-[6-(N-(tert-butoxycarbonyl)-amino-1-ethoxymethyl)pyridin-2-yl]propionamide.  
MS  $m/z$ : 352 (M+H).

30

2] N-Pivaloyl-2-amino-6-[(4-methylphenyl)-oxymethyl]-pyridine. MS  $m/z$ : 299 (M+H).

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3] *N*-Pivaloyl-2-amino-5-[(4-methylphenyl)-oxymethyl]pyridine. MS *m/z*: 299 (*M*+*H*).

5 **Preparation AB: *N*-Pivaloyl-2-amino-5-[1-morpholinylmethyl]pyridine**

*N*-Pivaloyl-2-amino-5-bromomethylpyridine (478 mg, 1.76 mmol) was dissolved in THF at 23°C with stirring and treated with morpholine (0.770 mL, 8.81 mmol) in a dropwise fashion. The resulting brown mixture was stirred at 23°C for 14 h. After stirring 14 h, the mixture was treated with saturated NaHCO<sub>3</sub> (2 mL) and stirred an additional 5 h at 23°C. After 5 h, the brown mixture was warmed to 55°C for 3 h, then cooled to RT and diluted with EtOAc (50 mL). The mixture was then washed with saturated NaHCO<sub>3</sub> (2X50 mL), dried (MgSO<sub>4</sub>), and concentrated to a brown residue which was immediately purified over silica gel (0 to 5% MeOH/CHCl<sub>3</sub>) to provide the title compound as a yellow oil. MS *m/z*: 278 (*M*+*H*).

**Preparation AC: 2-(Butyloxycarbonyl)amino-6-methylpyridine**

To a 2-L 3-neck Miller flask charged with 2-amino-6-methylpicoline (15 g, 138.7 mmol) and dry THF (1 L) was added di-*tert*-butyl dicarbonate (33.3 g, 152.6 mmol) then TEA (21.2 mL, 152.6 mmol) via addition funnel at 0°C. The reaction mixture was warmed to RT and added DMAP (1.7 g, 13.9 mmol). After 3.5 h, extracted with EtOAc, washed with saturated NH<sub>4</sub>Cl, H<sub>2</sub>O (3x), and brine (3x); dried (MgSO<sub>4</sub>) and concentrated in

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vacuo to afford the crude material as a turbid yellow oil. Trituration with hexane formed a precipitate which was filtered and the filtrate was concentrated in vacuo to give the title compound as a yellow oil.

5

**Preparation AD: 6-Bromomethyl-2-(butyloxycarbonyl)amino-pyridine**

To a solution of N-Boc-2-amino-6-picoline (28.7 g, 138 mmol) and CCl<sub>4</sub> (500 mL) was added NBS (27.1 g, 151.8 mmol) and AIBN (2.3 g, 13.8 mmol) and heated to reflux. After 2 h, added 0.1 equivalent of AIBN. The reaction mixture was heated at reflux for 20 h, filtered and concentrated in vacuo to give a dark oil. Purified by silica flash chromatography (100% hexane to 5% EtOAc/Hexane) to afford the desired as a yellow oil. MS m/z: 288.0 (M+H)

**Preparation AE: 2-(Butyloxycarbonyl)amino-6-cyanomethylpyridine**

To a solution of N-Boc-2-amino-6-methylbromidepyridine (12 g, 41.8 mmol) and EtOH (250 mL) was added NaCN (2 g, 41.8 mmol). The reaction mixture was heated to reflux for 2 h then cooled to RT and concentrated in vacuo. Purification by silica flash chromatography (100% Hexane to 20% EtOAc/Hexane) afforded the title compound as a yellow oil. MS m/z: 234.0 (M+H).

**Preparation AF: 2-Amino-6-cyanomethylpyridine**

To a solution of N-Boc-2-amino-6-methylnitrilepyridine and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added TFA

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(8 mL) and stirred at RT. After 3 h, the mixture was concentrated in vacuo, diluted with EtOAc and saturated NaHCO<sub>3</sub> was carefully added. The mixture was washed with saturated NaHCO<sub>3</sub> (2x) and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to afford the title compound as a yellow solid.

**Preparation AG: 6-Aminoethyl-2-(butyloxycarbonyl)amino-pyridine**

A solution of N-Boc-2-amino-6-methylnitrile-pyridine (1 g, 4.3 mmol) and EtOH (25 mL) was hydrogenated over 20% Pd(OH)<sub>2</sub>/C at RT and 40 psi. After 18 h, the mixture was filtered through Celite® and eluted with EtOAc. The filtrate was concentrated in vacuo to afford the title compound as a white foamy solid.

**Preparation AH: 2-Amino-6-(phthalimidyl)ethyl-pyridine**

To a solution of N-Boc-2-amino-6-ethylaminopyridine (1 g, 4.3 mmol) and CHCl<sub>3</sub> (25 mL) was added phthalic anhydride (0.64 g, 4.3 mmol). Heated to 70°C for 15 h then at RT for 5 days. The mixture was washed with H<sub>2</sub>O and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude N-Boc-2-amino-6-ethylphthalamidylpyridine, which was used without further purification. To a solution of crude N-Boc-2-amino-6-ethylphthalamidylpyridine (1.6 g, 4.3 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added 10 mL of TFA and the mixture was stirred at RT. After 30 min, the mixture was concentrated in vacuo. The residue was diluted with 90% MeOH/CH<sub>2</sub>Cl<sub>2</sub> and treated with solid NaHCO<sub>3</sub>, stirred

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for 15 min then filtered. The filtrate was concentrated in vacuo to afford the title compound as a yellow solid. MS m/z: 268.2 (M+H).

5 **Preparation AI: 2-[(6-Bromopyridin-2-yl)methylamino]-propan-1-ol**

To a stirred solution of the (6-bromo-2-pyridyl)-formaldehyde (0.52 g, 2.8 mmol) in toluene (14 mL) was added DL-2-amino-1-propanol (0.67 mL). The resulting mixture was heated to reflux with a Dean-Stark trap for 3 h under N<sub>2</sub> until complete formation of the imine was observed. The mixture was brought to RT followed by the addition of a solution of NaBH(OAc)<sub>3</sub> (2.0 g, 9.8 mmol) in AcOH (6 mL). The resulting mixture was stirred at RT and under N<sub>2</sub> for 56 h. The mixture was neutralized (pH 7.0) with a saturated solution of NaHCO<sub>3</sub> (aq) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50mL). The aqueous layer was concentrated by rotary evaporation and the residue obtained was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50mL). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated by rotary evaporation to afford the title compound as a pale yellow oil. EI-MS m/z 245 (M+H).

25 **Preparation AJ: (tert-Butoxy)-N-[(6-bromo(2-pyridyl)methyl)-N-(2-hydroxy-isopropyl)carboxamide**

To a stirred solution of 2-[(6-bromo-2-pyridyl)-methyl]aminopropan-1-ol (0.55 g, 2.2 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (11 mL) was added di-tert-butylidicarbonate (0.51 g, 2.42 mmol). The resulting mixture was stirred at RT and under N<sub>2</sub> for 15 h. The mixture was concentrated by

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rotary evaporation and purified on silica gel (2:1 hexanes/EtOAc, 5:95 MeOH/CH<sub>2</sub>Cl<sub>2</sub> and, 10:90 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) as eluent to afford the title compound as an off-white oil. EI-MS m/z 345 (M+H).

5

Preparation AK: (tert-Butoxy-N-[(6-bromo(2-pyridyl))-methyl]-N-(1-methyl-2-oxoethyl)carboxamide

To a dry flask was added oxalyl chloride (72  $\mu$ L) followed by the addition of dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The resulting colorless solution was brought to -63°C (dry ice/CHCl<sub>3</sub>) and a solution of DMSO (80  $\mu$ L) in 0.5 mL dry CH<sub>2</sub>Cl<sub>2</sub> was slowly added dropwise. A solution of (tert-butoxy)-N-[(6-bromo(2-pyridyl))methyl]-N-(2-hydroxy-isopropyl)carboxamide (0.19 g, 0.55 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), was added slowly drop wise. The resulting mixture was kept at -63°C and stirred for 30 min, followed by the slowly addition of a solution of TEA (0.31 mL) in dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL). The mixture was stirred at -63°C until all the starting material was consumed (checked by MS). The mixture was brought to -20°C, quenched with a saturated solution of NH<sub>4</sub>Cl (aq) and diluted with EtOAc. The organic phase was separated and the aqueous phase was extracted with EtOAc (3x20ml). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated by rotary evaporation to afford the title compound as a pale yellow semi-solid. EI-MS m/z 343 (M+H).

Preparation AL: N-[2-(diethylamino)-isopropyl](tert-butoxy)-N-[(6-bromo(2-pyridyl))methyl]-carboxamide

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To a stirred solution of (tert-butoxy-N-[(6-bromo(2-pyridyl)methyl)-N-(1-methyl-2-oxoethyl)-carboxamide (0.15 g, 0.44 mmol) in toluene (3 mL) was added DEA (0.2 mL). The resulting mixture was heated to  
5 reflux in a Dean-Stark trap under N<sub>2</sub> for 3 h. The mixture was brought to RT followed by the addition of a solution of NaBH(OAc)<sub>3</sub> (0.33 g, 1.54 mmol) in AcOH (6 mL). The yellow-solution was stirred at RT and under N<sub>2</sub> for 15 h. The mixture was diluted with EtOAc (20 mL)  
10 and washed with a saturated solution of NaHCO<sub>3</sub> (aq) (50 mL). The organic phase was separated, dried over MgSO<sub>4</sub>, filtered and concentrated by rotary evaporation to afford the title compound as a brown/ yellow oil. EI-MS m/z 400 (M+H).

15

**Preparation AM: N-[2-(diethylamino)isopropyl](tert-butoxy)-N-[(6-amino(2-pyridyl)methyl)-carboxamide**

To a stirred solution of N-[2-(diethylamino)-isopropyl](tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl)-carboxamide (80 mg 0.2 mmol) in IpOH (4 mL) in a sealed  
20 tube, was added NH<sub>4</sub>OH (28-30%, 6 mL) followed by an excess of Cu. The resulting solution was heated under pressure at 90°C for 24 h. The mixture was brought to RT, diluted with H<sub>2</sub>O (20 mL) and extracted with CHCl<sub>3</sub>  
25 (3x20mL). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated by rotary evaporation to afford the title compound as a pale-yellow oil. EI-MS m/z 337 (M+H).

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**Preparation AN: Methyl 2-[(6-bromo-2-pyridylmethyl)amino]-3-methyl-butyrate**

To a stirred solution of L-valine methyl ester  
5 hydrochloride (0.54 g, 3.24 mmol) in dry toluene (15 mL) at 80°C was added DIEA (2.0 mL 11 mmol) followed by (6-bromo-2-pyridyl)formaldehyde (0.50 g, 2.70 mmol). The resulting mixture was heated at 80°C for 3 h. The reaction was brought to RT and a solution of NaBH(OAc)<sub>3</sub>  
10 (1.4 g, 6.75 mmol) in glacial AcOH (4 mL) was added. The resulting mixture was stirred for 15 h and concentrated by rotary evaporation. The resulting yellow oil was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 ml), washed with a saturated solution of NaHCO<sub>3</sub>(aq) (50 mL), brine  
15 (50 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated by rotary evaporation and purified by flash chromatography (2:1 hexanes/EtOAc) to afford the title compound as a pale-yellow oil. EI-MS m/z 301 (M+H).

20 **Preparation AO: 2-[(6-Bromo-2-pyridylmethyl)amino]-3-methyl-butanol**

To a stirred solution of (tert-butoxy)-N-[(6-bromo(2-pyridyl))methyl]-N-[2-oxomethoxide-1-(methylethyl)-ethyl]carboxamide (0.47 g, 1.57 mmol) in  
25 dry toluene (25 mL) at -78°C was added dropwise diisobutylaluminum hydride 1.0 M solution in hexane (4.7 mL). The resulting brown-solution was stirred at -78°C for 3 h, brought to RT and stirred until (tert-butoxy)-N-[(6-bromo(2-pyridyl))methyl]-N-[2-oxomethoxide-1-(methylethyl)ethyl]carboxamide was  
30 consumed. The organic layer was separated, dried over

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Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated by rotary evaporation and purified on silica gel (10:90 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a yellow oil. EI-MS m/z 273 (M+H).

5

**Preparation AP: tert Butyl (6-bromopyridin-2-ylmethyl)-(1-hydroxymethyl-2-methyl-propyl)-carbamate**

To a stirred solution of 2-[(6-bromo-2-pyridylmethyl)amino]-3-methyl-butanol (0.30 g, 1.10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added di-tert-butyl dicarbonate (0.26 g, 1.21 mmol). The resulting solution was stirred for 15 h, concentrated by rotary evaporation and purified on silica gel (5:95 MeOH/CH<sub>2</sub>Cl<sub>2</sub> and 10:90 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a pale yellow solid. EI-MS m/z 373 (M+H).

15

**Preparation AQ: tert Butyl (6-bromopyridin-2-ylmethyl)-(1-formyl-2-methyl-propyl) carbamate**

To a flame-dried flask was added oxalyl chloride (70 µL) followed by the addition of dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The resulting colorless solution was brought to -63 °C (dry ice/CHCl<sub>3</sub>) and a solution of DMSO (70 µL) in 0.5 mL dry CH<sub>2</sub>Cl<sub>2</sub> was slowly added drop wise. The (tert-butoxy)-N-[(6-bromo(2-pyridyl))methyl]-N-[2-hydroxy -1-(methylethyl)ethyl]carboxamide (0.19 g, 0.51 mmol), previously dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), was added slowly dropwise. The resulting mixture was kept at -63°C and stirred for 30 min followed by the slowly addition of a solution of TEA (0.3 mL) in dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL). The mixture was stirred at -63°C until all the starting material was consumed (checked by MS) (1.5 h).

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The mixture was brought to -20°C, quenched with a saturated solution of NH<sub>4</sub>Cl (15 mL) and diluted with EtOAc (35 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3x30mL). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated by rotary evaporation without further purification to afford the title compound as a yellow-semi solid. EI-MS m/z 371 (M+H).

10 Preparation AR: tert-Butyl (6-bromopyridin-2-ylmethyl)-(1-diethylaminomethyl-2-methyl-propyl)carbamate

To a stirred solution of (tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl]-N-[1-(methylethyl)-2-oxoethyl]carboxamide (0.17 g, 0.46 mmol) in toluene (5 mL) was added DEA (0.14 mL). The resulting mixture was heated to reflux in a Dean-Stark trap under N<sub>2</sub> for 3 h. The mixture was brought to RT followed by the addition of a solution of NaBH(OAc)<sub>3</sub> (0.34 g, 1.61 mmol) in glacial AcOH (6 mL). The yellow-solution was stirred at RT and under N<sub>2</sub> for 15 h. The mixture was diluted with EtOAc (20 mL) and washed with a saturated solution of NaHCO<sub>3</sub> (aq) (15 mL). The aqueous layer was separated and concentrated under reduced pressure. The solid obtained was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were combined, dried over MgSO<sub>4</sub>, filtered and, concentrated by rotary evaporation to afford the title compound as a pale yellow oil. EI-MS m/z 428 (M+H).

20 Preparation AS: tert-Butyl (6-aminopyridin-2-ylmethyl)-(1-diethylaminomethyl-2-methyl-propyl)carbamate

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To a stirred solution of N-{1-[(diethylamino)-methyl]-2-methylpropyl}(tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl)carboxamide (5 mg, 0.012 mmol) in IpOH (5 mL) in a sealed tube, was added  $\text{NH}_4\text{OH}$  (28-30% 6 mL) followed by excess Cu. The resulting solution was heated under pressure at 90°C for 24 h. The mixture was brought to RT, diluted with  $\text{H}_2\text{O}$  (10 mL) and extracted with  $\text{CHCl}_3$  (3x20mL). The organic layers were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated by rotary evaporation to afford the title compound as a green oil. No purification was required. EI-MS m/z 365 (M+H).

**Preparation AT: 2-Bromo-6-(piperidin-1-**

**ylmethyl)pyridine**

To a stirred solution of 6-bromo-2-pyridine carboxaldehyde (5.05 g, 27 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (200 ml) at RT, under  $\text{N}_2$ , piperidine (2.95 ml, 29 mmol) was added, followed by  $\text{NaBH}(\text{OAc})_3$  (11.51 g, 54 mmol) and AcOH (6.2 ml, 108 mmol) 30 min later. After 20 h, a 2M solution of  $\text{Na}_2\text{CO}_3(\text{aq})$  (20 ml) was added. The mixture was vigorously stirred for an additional 30 min, washed successively with a saturated solution of  $\text{NaHCO}_3(\text{aq})$  until the pH of the aqueous layer reached 7 (2x100ml),  $\text{H}_2\text{O}$  (100 ml) and brine (100 ml). The organic layer was separated, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to yield the title compound as a yellow oil. This was used crude in the next step. MS m/z: 255 (M+H), 257 (M+3).

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Preparation AU: 2-Amino-6-(piperidin-1-ylmethyl)pyridine

To a solution of 2-bromo-6-(piperidylmethyl)pyridine (5.21 g, 20 mmol) in propan-2-ol (30 ml) in a sealed tube at RT a catalytic amount of Cu (100 mg) and 28-30% NH<sub>4</sub>OH (35 ml) were added. The stirred suspension was heated to 95°C for 40 h. After cooling to RT, the reaction mixture was diluted with H<sub>2</sub>O (100 ml) and extracted with EtOAc (4x80ml). The organic layers were combined, then washed with H<sub>2</sub>O (50 ml) followed by brine (50 ml). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to yield the title compound (as a dark yellow oil. This was used as crude. MS m/z: 193 (M+H)+.

Preparation AV: Ethyl 2-(4-aminosulfonylphenyl)thiazole-4-carboxylate

In an oven-dried, 100-mL, round-bottomed flask were placed 4-cyanobenzenesulphonamide (4.1 g, 22.50 mmol), TEA (5 mL) in pyridine (40 mL). H<sub>2</sub>S was bubbled through this mixture for 1 h at RT. The reaction was diluted with EtOAc (125 mL) and H<sub>2</sub>O (50 mL). The phases were separated, and the organic layer was washed with H<sub>2</sub>O (4x25 mL) and brine (15 mL), dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to afford the crude thiobenzamide as an oily solid; MS m/z: 217 (M+H). In an oven-dried, 100-mL, round-bottomed flask were placed the crude thiobenzamide, ethyl bromopyruvate (3.0 mL, 23.66 mmol) in EtOH (40 mL). The reaction was heated to 75°C for 12 h, then cooled to RT. The mixture was

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concentrated *in vacuo* to give the crude sulfonamide as a yellow solid which was filtered, washed with H<sub>2</sub>O (1x10 mL) and Et<sub>2</sub>O (4x10 mL) to afford the title compound as a yellow solid. MS m/z: 313 (M+H).

5

**Preparation AW: 2-(4-Aminosulfonylphenyl)thiazole-4-carboxylic acid**

In an oven-dried, 100-mL, round-bottomed flask was placed ethyl 2-(4-aminosulfonylphenyl)thiazole-4-  
10 carboxylate (1300 mg, 4.2 mmol), LiOH monohydrate (350 mg, 8.3 mmol) in MeOH (40 mL) and H<sub>2</sub>O (4 mL). The solution was heated to 75°C for 3 h, cooled to RT, and concentrated. The resulted yellow solid was dissolved in H<sub>2</sub>O (10 mL), extracted with EtOAc (1x15 mL). The  
15 aqueous layer was acidified with 2N aqueous HCl (4.15 mL). The precipitate was filtered, and washed with H<sub>2</sub>O (10 mL) to afford the title compound as a light-yellow solid. MS m/z: 285 (M+H).

20 **Preparation AX: 2-(4-(4-morpholinyl)sulfonylphenyl)-thiazole-4-carboxylic acid**

In a manner similar to that described for the preparation of 2-(4-aminosulfonylphenyl)thiazole-4-carboxylic acid, 460 mg of 4-(morpholinosulfonyl)-  
25 benzonitrile was treated with H<sub>2</sub>S, ethyl bromopyruvate, and LiOH successively to give the title compound. MS m/z: 355 (M+H).

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**Preparation AY: 2-(4-Boc-aminophenyl)-thiazole-4-carboxylic acid**

In a manner similar to that described for the  
5 preparation of 2-(4-aminosulfonylphenyl)thiazole-4-carboxylic acid, 4-[(1,1-dimethylethoxy)carbonyl]-aminobenzonitrile was treated with H<sub>2</sub>S, ethyl bromopyruvate, and LiOH successively to give the title compound. MS m/z: 321 (M+H).

10

**Preparation AZ: Ethyl 2-(phenoxy)thiazole-4-carboxylate**

A mixture of the bromothiazole (1.03 g, 4.36 mmol) and phenol (10.0 g, 106 mmol) was stirred at 180°C for 1 h, cooled to RT, diluted with 100 ml of EtOAc, washed  
15 with 1N NaOH (40x3), H<sub>2</sub>O, and brine, then dried over MgSO<sub>4</sub>, and concentrated in vacuo to yield a light yellow residue. Purification over silica gel (gradient, 5% to 10% EtOAc/hexanes) provided the title compound. MS m/z: 250 (M+H)+.

20

**Preparation BA: 2-(Phenoxy)thiazol-4-ylcarbonylazide**

TEA (0.17 ml, 1.20 mmol) was added to a solution of the thiazole carboxylic acid (0.13 g, 0.59 mmol) in 10 ml of THF at 0 °C. The mixture was stirred at 0°C  
25 for 20 min whereupon ethyl chloroformate (0.065 ml, 0.65 mmol) was added. After the mixture was stirred for 30 min, a solution of NaN<sub>3</sub> (0.043 g, 0.65 mmol) in 3 ml of H<sub>2</sub>O was added, the reaction was stirred for 30 min, then warmed to RT, diluted with 25 ml of H<sub>2</sub>O, and  
30 extracted with EtOAc. The combined organic portions were washed with brine, dried over MgSO<sub>4</sub>, filtered, and

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removal of the solvents in vacuo yielded the title compound as a light brownish solid. MS m/z: 247 (M+H).

**Preparation BB: 6-Chloro-thionicotinamide**

- 5 To a solution of the 4-chloronicotinamide (5 g, 31.9 mmol) and dry THF (200 mL) was added P<sub>2</sub>S<sub>5</sub> (15.6 g, 35.1 mmol) and Na<sub>2</sub>CO<sub>3</sub> (3.7 g, 35.1 mmol). The mixture was heated at reflux for 1.5 h, cooled reaction mixture to RT and filtered off a yellow solid. The filtrate  
10 was extracted with EtOAc, washed with H<sub>2</sub>O and brine; dried (MgSO<sub>4</sub>) then concentrated in vacuo to give the title compound as a yellow solid. MS m/z: 173.0 (M+H).

15 **Preparation BC: Ethyl 2-(6-chloro-3-pyridyl)thiazole-4-carboxylate**

- To a mixture of the 4-chloro-thionicotinamide (5.5 g, 31.9 mmol) and EtOH (300 mL) was added bromo-ethyl-pyruvate (4.4 mL, 35.1 mmol). The mixture was heated  
20 at reflux for 15 h, cooled and concentrated in vacuo to afford a yellow solid/orange oil. The oil was diluted with EtOAc and filtered off yellow solid. The filtrate was filtered through Celite® and concentrated in vacuo to give a dark yellow oil. The oil was diluted with 2%  
25 MeOH/CH<sub>2</sub>Cl<sub>2</sub> and filtered through a pad of silica gel (150 mL). Elution with 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> (500 mL), followed by concentration in vacuo afforded the title compound as a yellow crystalline solid. MS m/z: 269.1 (M+H).

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**Preparation BD: 2-(6-Methoxy-3-pyridyl)thiazole-4-carboxylic acid**

To a solution of the ethyl 2-(6-chloro-3-pyridyl)thiazole-4-carboxylate (0.61 g, 2.3 mmol) and MeOH (50 mL) was added solid NaOMe (135 mg, 2.5 mmol) and stirred at RT. After 3 h the ethyl ester transesterified to the methyl ester. NaOMe (1 eq, 135 mg) was added and the mixture was heated to reflux. After 15 h, the ester hydrolyzed to the 2-(6-chloro-3-pyridyl)thiazole carboxylic acid. NaOMe (2 eq) was added and the reaction was heated at reflux for 18 h. The mixture was acidified to pH 5 with concentrated HCl, extracted with EtOAc, washed with H<sub>2</sub>O and brine; dried (MgSO<sub>4</sub>) and concentrated in vacuo to give the desired carboxylic acid as a yellow solid. MS m/z: 237.1 (M+H).

**Preparation BE: 2-(2-Chloropyridin-4-yl)thiazole-4-carbonyl azide**

A mixture of 3-(3-chloro-4-pyridyl)-4-thiazole carboxylic acid (0.6 g, 2.5 mmol) and dry THF (20 mL) was cooled to 0°C with stirring. TEA (0.7 mL, 5.0 mmol) was added and the reaction mixture was stirred for 20 min. Ethyl chloroformate (0.24 mL, 2.5 mmol) was added and the solution was stirred for 30 min. A solution of NaN<sub>3</sub> (174 mg, 2.7 mmol) in 3 mL of H<sub>2</sub>O was added and the reaction mixture was warmed to RT. After 30 min, 10 mL of H<sub>2</sub>O was added and the mixture was extracted with EtOAc (3x), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give the title compound as a pink solid. MS m/z: 266.0 (M+H)+

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**Preparation BF: Ethyl 2-(3-methoxyphenyl)-thiazole-4-carboxylate**

A suspension of 3-methoxyphenyl boronic acid (0.25 g, 1.65 mmol), ethyl 2-bromothiazole-4-carboxylate (0.33 g, 1.4 mmol),  $\text{PdCl}_2(\text{dppf})_2$  (0.11 g) and 2M  $\text{Na}_2\text{CO}_3$  (aq) (2 mL) in DME (10 mL) was heated to reflux for 20 h. The mixture was cooled to RT, filtered, concentrated by rotary evaporation and purified on silica gel (6:1 hexanes/EtOAc and 4:1 hexanes/EtOAc) to afford the title compound as a light-brown oil. EI-MS m/z 264 (M+H).

**Preparation BG: 2-(3-Methoxyphenyl)thiazole-4-carboxylic acid**

To a stirred solution of the ethyl 2-(3-methoxyphenyl)thiazole-4-carboxylate (0.23 g, 0.87 mmol) in EtOH (10 mL) was added 1N NaOH (aq) (5 mL). The resulting mixture was heated to reflux until the starting material was consumed (2 h). The mixture was cooled to RT, acidified with 1N HCl (aq) and concentrated by rotary evaporation. The residue was extracted with  $\text{CH}_2\text{Cl}_2$  (3x15mL). The extracts were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated by rotary evaporation to afford the title compound as an off-white solid. EI-MS m/z 236 (M+H).

**Preparation BH: Ethyl 2-(2-methoxyphenyl)-thiazole-4-carboxylate**

A suspension of 2-methoxyphenyl boronic acid (0.25 g, 1.65 mmol), ethyl 2-bromothiazole-4-carboxylate

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(0.33 g, 1.4 mmol),  $\text{PdCl}_2(\text{dppf})_2$  (0.11 g, 0.14 mmol) and 2M  $\text{Na}_2\text{CO}_3(\text{aq})$  (2 mL) in DME (10 mL) was heated at reflux for 20 h, cooled to RT, filtered, concentrated by rotary evaporation and purified on silica gel (6:1  
5 hexanes/EtOAc and 4:1 hexanes/EtOAc) to afford the title compound as a light-brown oil. EI-MS  $m/z$  264 (M+H).

**Preparation BI: 2-(2-Methoxyphenyl)thiazole-4-carboxylic acid**

To a stirred solution of ethyl 2-(2-methoxyphenyl)thiazole-4-carboxylate (0.27 g, 1.03 mmol) in EtOH (10 mL) was added 1N NaOH (aq) (5 mL). The resulting mixture was heated to reflux for 2 h. The  
15 mixture was cooled to RT, acidified with 1N HCl (aq) and concentrated by rotary evaporation. The residue was extracted with  $\text{CH}_2\text{Cl}_2$  (3x15mL). The extracts were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated by rotary evaporation to afford the title compound as  
20 an off-white solid. EI-MS  $m/z$  236 (M+H).

**Preparation BJ: 2-[(4-Methoxyphenoxy)methyl]thiazole-4-carboxylic acid**

To a stirred solution of ethyl 2-(4-methoxyphenoxy)methylthiazole-4-carboxylate (0.10 g, 0.34 mmol) in EtOH (5 mL) was added 1N NaOH (2.0 mL) and was heated to reflux until the starting material was consumed (2 h). The mixture was brought to RT, acidified with 1N HCl (pH 4.0) and concentrated by  
25 rotary evaporation. The residue obtained was  
30 partitioned between EtOAc (50 mL) and  $\text{H}_2\text{O}$  (30 mL). The

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organic phase was separated, dried over  $\text{MgSO}_4$ , filtered and concentrated by rotary evaporation to afford the title compound as a white solid. EI-MS  $m/z$  266 (M+H).

5 **Preparation BK: Ethyl 2-aminothiazole-4-carboxylate**

To a stirred suspension of thiourea (23.03 g, 0.30 mol) in EtOH (320 ml) at RT, under  $\text{N}_2$ , ethyl bromopyruvate (59.0 g, 0.30 mol) was added dropwise. The solution was then heated at  $45^\circ\text{C}$  for 12 h. After  
10 cooling to RT the reaction flask was placed in the fridge overnight. The resulting solid was filtered, washed with cold EtOH (3x50ml) then air dried to yield the title compound as a pale yellow amorphous solid. MS  $m/z$ : 173 (M+H).

15

**Preparation BL: 2-Bromothiazole-4-carboxylic acid**

To a well stirred suspension of ethyl 2-aminothiazole-4-carboxylate hydrobromide (29.99 g, 0.17 mol) in 16% HBr(aq) (400 ml) at  $0^\circ\text{C}$ , a solution of  
20  $\text{NaNO}_2$  (12.49 g, 0.18 mol) in  $\text{H}_2\text{O}$  (22 ml) was added dropwise. The mixture was maintained at  $0^\circ\text{C}$  for an additional 35 min then CuBr (28.23 g, 0.20 mol) and an additional volume of 16% HBr(aq) (150 ml) were added. The ice bath was removed and the suspension heated to  
25  $70^\circ\text{C}$  for 1 hr. The mixture was filtered hot. The filtrate was saturated with NaCl then extracted with EtOAc (2x400ml). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude brown oil/solid residue  
30 was used directly in the next step. A solution of the brown residue in EtOH (100 ml) and 1M NaOH (aq) (367

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ml, 0.36 mol) was stirred and heated at reflux for 1 h. The reaction mixture was filtered then extracted with EtOAc (100 ml). The aqueous layer was separated and concentrated under reduced pressure to remove the remaining EtOH. The aqueous solution was acidified to pH 1 with 2N HCl(aq). The solid was filtered off and air dried to yield the title compound as a beige amorphous solid. MS m/z: 208 (M+H) 210 (M+3).

10 Preparation BM: Ethyl 2-(2,6-dichloro-4-pyridyl)thiazole-4-carboxylate

2,6-Dichloropyridine-4-thiocarboxamide (1.0 g, 4.83 mmol) was dissolved in dry 1,4-dioxane followed by adding ethyl bromopyruvate (0.9 mL, 7.24 mmol) and pyridine (0.4 mL, 4.83 mmol). The resulting mixture was heated to reflux under N<sub>2</sub> for 5 h. After cooling to RT, solvent was removed. The residue was extracted with CHCl<sub>3</sub>. The organic layer was washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, and concentrated to give a brownish solid. This crude was purified by chromatography on silica gel. Elution with hexane:acetone (90:10) gave a title compound as yellow solid. MS m/z: 303 (M+H). Calc'd. for C<sub>11</sub>H<sub>8</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S - 303.16.

25

Preparation BN: 2-(2,6-Dichloro-4-pyridyl)thiazole-4-carboxylic acid

2-(2,6-Dichloropyridin-4-yl)-ethylthiazolo-4-carboxylate (500 mg, 1.65 mmol) was dissolved in MeOH (10 mL) followed by adding 1N NaOH (2.5 mL, 2.47 mmol). The resulting mixture was stirred at RT for 4 h. The

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pH was adjusted to 5 using 1N HCl. The solvent was removed in vacuo and the residue was partitioned between EtOAc and H<sub>2</sub>O. The aqueous layer was extracted more with EtOAc. The combined organic layers was dried  
5 over MgSO<sub>4</sub> and concentrated to give a white solid. MS *m/z*: 275.1 (M+H). Calc'd. for C<sub>9</sub>H<sub>4</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S - 275.11.

**Preparation B0: Ethyl 6-[2-(2,2,2-trifluoroethoxy)-3-pyridyl]thiazole-4-carboxylate**

10 6-(2,2,2-Trifluoroethoxy)pyridine-3-thiocarboxamide (800 mg, 3.4 mmol), ethyl bromopyruvate (0.9 mL, 6.8 mmol), and pyridine (0.3 mL, 3.4 mmol) were heated at reflux in dry 1,4-dioxane (20 mL) to yield title compound as pale yellow solid. MS *m/z*:  
15 333.1 (M+H). Calc'd. for C<sub>13</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S - 332.3.

**Preparation BP: 6-[2-(2,2,2-trifluoroethoxy)-3-pyridyl]thiazole-4-carboxylic acid**

Ethyl 6-[2-(2,2,2-trifluoroethoxy)-3-pyridyl]thiazole-4-carboxylate (750 mg, 2.25 mmol) and  
20 1N NaOH (3.4 mL, 3.4 mmol) were dissolved in MeOH (10 mL) to afford the title compound as a white solid. MS *m/z*: 305.1 (M+H). Calc'd. for C<sub>11</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S - 304.25.

25 **Preparation BQ: 2-(Phenoxy)thiazole-4-carboxylic acid**

A mixture of ethyl 2-phenoxythiazole-4-carboxylate (0.17 g, 0.68 mmol) and LiOH monohydrate (0.14 g, 3.40 mmol) in 2 ml of MeOH, 2 ml of H<sub>2</sub>O, and 2 ml of THF was stirred at RT overnight, the solvents were removed in  
30 vacuo and the residue was diluted with water. The aqueous mixture was acidified with 1N HCl (aq) to pH=1-

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2, then extracted with EtOAc, the combined organic portions were washed with brine, dried over  $\text{MgSO}_4$ , filtered, removal of the solvents in vacuo yielded the title compound as a white solid. EI-MS = 222.4

5 (M+H)+. Calc'd for  $\text{C}_{10}\text{H}_7\text{NO}_3\text{S}$ : 221.01.

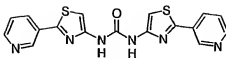
**Preparation BR: 3-(3-Nitrophenyl)pyridine**

To a 1-iodo-3-nitrobenzene (1.0 g, 4.01 mmol) in dry DME (20 mL) was added pyridine-3-boronic acid (641  
10 mg, 5.22 mmol),  $\text{PdCl}_2\text{dppf}$  (327 mg, 0.40 mmol), and 2M  $\text{Na}_2\text{CO}_3$  (3.0 mL). The resulting mixture was heated to reflux under  $\text{N}_2$  for 15 h. Solvent was separated from inorganic solid by filtration. The solvent was removed and the residue was extracted with  $\text{CHCl}_3$ . The organic  
15 layer was washed with water, brine, and dried over  $\text{MgSO}_4$ . The solvent was removed to give dark brown solid which was purified by chromatography on silica gel. Elution with Hexane:acetone mixture (80:20) gave the final compound as a tan solid. MS m/z: 201.3  
20 (M+H). Calc'd. for  $\text{C}_{11}\text{H}_8\text{N}_2\text{O}_2$  - 200.23.

**Preparation BS: 3-(3-Aminophenyl)pyridine**

To a prehydrogenated solution of  $\text{Pd}(\text{OH})_2$  (298 mg, 2.12 mmol) in EtOH (10 mL) was added 3-(3-pyrid-1-yl)-  
25 1-nitrobenzene (440 mg, 2.12 mmol) in EtOH (10 mL). The resulting mixture was stirred at RT under  $\text{H}_2$  for 2 h. Solvent was separated from  $\text{Pd}(\text{OH})_2$  by filtration through Celite®. Solvent was then removed to give final compound as pale yellow solid. MS m/z: 171.3  
30 (M+H). Calc'd. for  $\text{C}_{11}\text{H}_{10}\text{N}_2$  - 170.22.

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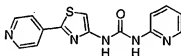
**Example 1**

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**N,N'-bis [2-(3-Pyridinyl)-4-thiazolyl] urea**

To a 50 mL round bottomed flask were added 0.106 g (0.458 mmol) of 2-(3-pyridinyl)-4-thiazolyl-carbonylazide, toluene (10 mL) and 5 drops of H<sub>2</sub>O. The mixture was heated at 95°C for 4 h then cooled to RT. The precipitate that formed was filtered, washed with a minimum amount of toluene and dried under high vacuum to give the product as a pale yellow solid. MS m/z: 381.5 (M+H). Calc'd. for C<sub>14</sub>H<sub>12</sub>N<sub>6</sub>OS<sub>2</sub> - 380.453.

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**Example 2**

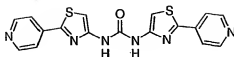
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**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-pyridinylurea**

To a solution of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (60 mg, 0.260 mmol) in 10 mL toluene was added 2-aminopyridine (35 mg, 0.372 mmol). The mixture was heated at 95 °C for 18 h then cooled to RT and filtered. The precipitate was washed with toluene (3mL) and dried under high vacuum to give the product as a pale yellow solid. MS m/z: 298.5 (M+H). Calc'd. for C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>OS - 297.341.

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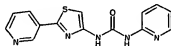
- 156 -

Example 35      **N,N'-bis [2-(4-Pyridinyl)-4-thiazolyl] urea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (130 mg, 0.562 mmol) was heated in toluene (10 mL) containing 4  
10 drops of H<sub>2</sub>O to give the product as a pale yellow solid. MS m/z: 381.5 (M+H). Calc'd. for C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>OS<sub>2</sub> - 380.453.

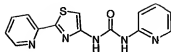
Example 4

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**N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-pyridinylurea**

20      In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (48 mg, 0.208 mmol) and 2-aminopyridine (24 mg, 0.255 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS m/z: 298.4 (M+H). Calc'd. for  
25 C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>OS - 297.341.

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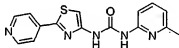
Example 5

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**N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-pyridinylurea**

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200 mg, 0.87mmol) and 2-aminopyridine (318 mg, 2.6 mmol) were heated in toluene (10 mL) at 100°C for 14 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et<sub>2</sub>O (2x10mL) and cold EtOAc (3x5 mL). The solid was recrystallized from EtOAc to afford the product as an off-white solid: m.p. 233-235°C. MS m/z: 298 (M+H). Calc'd for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>OS 297.341.

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Example 6

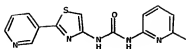
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**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(6-methylpyridinyl)urea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (69 mg, 0.298 mmol) and 2-amino-6-methylpyridine (101 mg, 0.934 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS m/z: 312.5 (M+H). Calc'd. for C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>OS - 311.368.

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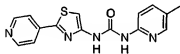
Example 7

5                   **N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-(6-methylpyridinyl)urea**

In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (78 mg, 0.337 mmol) and 2-amino-6-methylpyridine (101 mg, 0.934 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 312.2 (M+H). Calc'd. for  $C_{15}H_{13}N_5OS$  - 311.368.

10

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Example 8

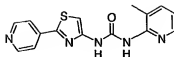
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**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(5-methylpyridinyl)urea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (72 mg, 0.311 mmol) and 2-amino-5-methylpyridine (106 mg, 0.981 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 312.5 (M+H). Calc'd. for  $C_{15}H_{13}N_5OS$  - 311.368.

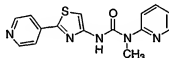
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Example 95                    **N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(3-methylpyridinyl)urea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (135 mg, 0.584 mmol) and 2-amino-3-methylpyridine (200 mg, 1.98 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS m/z: 312.4 (M+H). Calc'd. for  $C_{15}H_{13}N_5OS$  - 311.368.

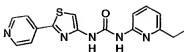
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Example 1020                    **N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-pyridinyl-N'-methylurea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (71 mg, 0.310 mmol) and 2-methylaminopyridine (210 mg, 1.94 mmol) were heated in toluene (7 mL) to give the product as pale yellow crystals. MS m/z: 312.5 (M+H). Calc'd. for  $C_{15}H_{13}N_5OS$  - 311.368.

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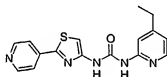
Example 11

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**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea**

10 In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (75 mg, 0.324 mmol) and 2-amino-6-ethylpyridine (200 mg, 1.63 mmol) were heated in toluene (8 mL) to give the product as a pale yellow solid. MS  $m/z$ : 326.5 (M+H). Calc'd. for  $C_{16}H_{15}N_5OS$  - 325.395.

15

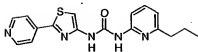
Example 12

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**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea**

25 In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (82 mg, 0.355 mmol) and 2-amino-4-ethylpyridine (106 mg, 0.867 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 326.5 (M+H). Calc'd. for  $C_{16}H_{15}N_5OS$  - 325.395.

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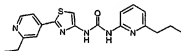
**Example 13**

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**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea**

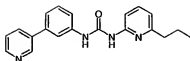
In a manner similar to that described in Example  
10 3, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (89 mg,  
0.385 mmol) and 2-amino-6-(n-propyl)pyridine (171 mg,  
1.25 mmol) were heated in toluene (10 mL) to give the  
product as a pale yellow solid. MS  $m/z$ : 339.4 (M+H).  
Calc'd. for  $C_{17}H_{17}N_5OS$  - 339.422.

15

**Example 14****N-[2-(2-Ethyl-4-pyridinyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea**

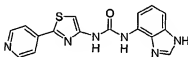
In a manner similar to that described in Example  
6, 2-(4-(2-ethyl)-pyridinyl)-4-thiazolylcarbonylazide  
25 (460mg, 1.77mmol) and 2-amino-6-(n-propyl)pyridine  
(483mg, 3.55 mmol) were heated in toluene (20 mL) at  
100°C for 14 h. After cooling to RT, the solids were  
collected by filtration and washed first with toluene  
(2 x 20 mL) followed by EtOAc:Et<sub>2</sub>O (4:1) (4 x 20 mL) to  
30 give the product as an off-white solid: m.p. 204-206°C.  
MS  $m/z$ : 368 (M+H). Calc'd. for  $C_{19}H_{21}N_5OS$  - 367.476.

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**Example 15****5 N-[3-(3-Pyridinyl)phenyl]-N'-2-(6-propylpyridinyl)urea**

To a suspended anhydrous solution of 3-pyridylaniline (90 mg, 0.53 mmol) in dry toluene (4 mL) was added phosgene (0.36 mL, 0.69 mmol, 20% in toluene) followed by DIEA (0.20 mL, 1.05 mmol) under an atmosphere of argon. After stirring for 0.5 h at RT, 2-amino-6-n-propylpyridine (72 mg, 0.53 mmol) in dry toluene (4 mL) was added dropwise into the mixture. The resulting mixture was stirred at RT for 18 h. The organic solvent was removed under vacuum. The residue was purified by chromatography on flash silica gel using 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluant to obtain the final urea as an off-white solid. MS m/z : 333.4 (M+H). Calc'd. for C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>O - 332.405.

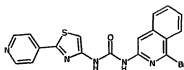
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**Example 16****25 N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-4-benzimidazolylurea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (32 mg, 0.138 mmol) and 4-aminobenzimidazole (32 mg, 0.240 mmol) were heated in toluene (8 mL). The crude product was recrystallized with CH<sub>3</sub>CN:MeOH (~ 10:1) to give the

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product as a pale brown solid. MS  $m/z$ : 337.5 (M+H).  
Calc'd. for  $C_{16}H_{12}N_6OS$  - 336.378.

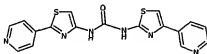
**Example 17**

**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-3-(1-bromoisoquinolinyl)urea**

10

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (61 mg, 0.264 mmol) and 3-amino-1-bromo-isoquinoline (120 mg, 0.538 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 427.2 (M+H).  
Calc'd. for  $C_{18}H_{12}BrN_7OS$  - 426.297.

15

**Example 18**

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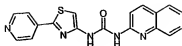
**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-[4-(3-pyridinyl)-2-thiazolyl] urea**

25

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (36 mg, 0.298 mmol) and 2-amino-4-(3-pyridyl)-thiazole (29 mg, 163 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 381.5 (M+H).  
Calc. for  $C_{21}H_{12}N_8OS_2$  - 380.453.

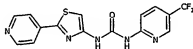
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**Example 19****5 N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-quinolinyurea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (38 mg, 0.164 mmol) and 2-aminoquinoline (53 mg, 0.370 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 348.4 (M+H). Calc. for  $C_{18}H_{13}N_5OS$  - 347.401.

10

**Example 20**

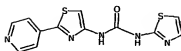
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**20 N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(5-trifluoromethylpyridinyl)urea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (40 mg, 0.173 mmol) and 2-amino-5-trifluoromethylpyridine (165 mg, 1.02 mmol) were heated in 10 mL toluene to give the product as a pale yellow solid. MS  $m/z$ : 366.3 (M+H). Calc'd. for  $C_{15}H_{10}F_3N_5OS$  - 365.339.

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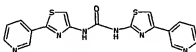
Example 21

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**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-thiazolylurea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (70 mg, 0.303 mmol) and 2-aminothiazole (38 mg, 0.38 mmol) were heated in toluene (12 mL) to give the product as a pale yellow solid. MS  $m/z$ : 304.4 (M+H). Calc'd. for  $C_{12}H_8N_6OS_2$  - 303.366.

15

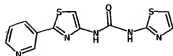
Example 22**N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-[4-(3-pyridinyl)-2-thiazolyl] urea**

20

In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (36 mg, 0.156 mmol) and 2-amino-4-(3-pyridinyl)thiazole (30 mg, 0.169 mmol) were heated in toluene (8 mL) to give the product as a pale yellow solid. MS  $m/z$ : 381.5 (M+H). Calc'd. for  $C_{17}H_{12}N_6OS_2$  - 380.453.

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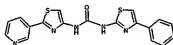
**Example 23**

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**N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-thiazolylurea**

In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (59 mg, 0.255 mmol) and 2-aminothiazole (27 mg, 268 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 304.3 (M+H). Calc'd. for  $C_{11}H_8N_4OS_2$  - 303.366.

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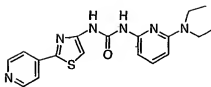
**Example 24**

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**N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-[4-phenyl-2-thiazolyl]urea**

In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (49 mg, 0.211 mmol) and 2-amino-4-phenylthiazole (39 mg, 0.218 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 380.5 (M+H). Calc'd. for  $C_{18}H_{13}N_4OS_2$  - 379.465.

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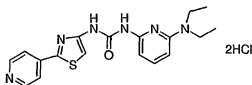
**Example 25**

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**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-  
diethylamino)pyridinyl]urea**

A mixture of 2-(4-pyridinyl)-4-thiazolyl-  
 10 carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(N,N-  
 diethylamino)pyridine (150 mg, 0.91 mmol) in toluene (3  
 mL) was heated at 70°C for 1 h, and then at 80°C for 5  
 h. After the mixture was cooled to RT the solvent was  
 removed in vacuo and the crude product was purified by  
 15 chromatography on silica gel (1:10 MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to  
 give N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-  
 diethylamino)pyridinyl]urea. MS m/z: 369 (M+1).  
 Calc'd. for C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>OS - 368.463.

20

**Example 26**

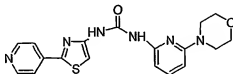
25

**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-  
diethylamino)pyridinyl]urea hydrochloride**

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-  
 diethylamino)pyridinyl]urea (Example 25) was dissolved  
 in 5 ml of MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:1) and (1 M) HCl (8 mL) in

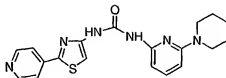
- 168 -

Et<sub>2</sub>O solution was added. The solvents were removed in vacuo to afford the title salt as a yellow solid.

**Example 27**

**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(4-morpholinyl)pyridinyl]urea**

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(4-morpholinyl)pyridine (150 mg, 0.84 mmol) in toluene (5 mL) was heated at 80°C for 5 h. After the mixture was cooled to RT the solvent was removed in vacuo and the crude product was purified by chromatography on silica gel (1:10 MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a light yellow solid. MS m/z: 383 (M+1). Calc'd. for C<sub>18</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub>S - 382.446.

**Example 28**

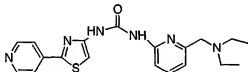
**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-piperidinyl)pyridinyl]urea**

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(1-piperidinyl)pyridine (100 mg, 0.56 mmol) in toluene (3

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mL) was heated at 80°C for 4 h. After cooling to RT, H<sub>2</sub>O was added and the mixture was extracted with EtOAc (3x80 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel (1:20 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a light yellow solid. MS m/z: 381 (M+1). Calc'd for C<sub>19</sub>H<sub>20</sub>N<sub>6</sub>OS - 380.475.

10

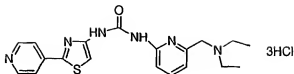
Example 29

15

**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N,N-diethylaminomethyl)pyridinyl]urea**

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(N,N-diethylaminomethyl)pyridine (150 mg, 0.84 mmol) in toluene (5 mL) was heated at 80°C for 5 h. After the mixture was cooled to RT the solvent was removed in vacuo and the crude product was purified by chromatography on silica gel (1:10 MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to give the base. MS m/z: 383 (M+1). Calc'd. for C<sub>19</sub>H<sub>22</sub>N<sub>6</sub>OS - 382.49.

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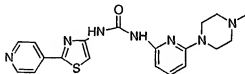
Example 30

5

**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-diethylaminomethylamino)pyridinyl]urea hydrochloride**

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N",N"-diethylaminomethylamino)pyridinyl]urea (Example 29) was dissolved in 5 ml of MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:1) and 1M HCl (8 mL) in Et<sub>2</sub>O solution was added. The solvents were removed in vacuo to afford the title salt as a yellow solid.

15

Example 31

**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-methyl-4-piperazinyl)pyridinyl]urea**

20

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(1-(4-methyl)piperazinyl)pyridine (100 mg, 5.21 mmol) in toluene (5 mL) was heated at 80°C for 5 h. After the mixture was cooled to RT the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (1:10 MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to give N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(1-methyl-4-

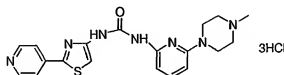
25

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piperazinyl]pyridinyl]urea. m.p. 251-253°C. MS  $m/z$ : 396 (M+1). Calc'd. for  $C_{19}H_{22}N_6OS$  - 395.489.

**Example 32**

5

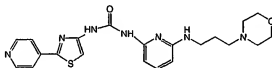


**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-methyl-4-piperazinyl)pyridinyl]urea hydrochloride**

10

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-methyl-4-piperazinyl)pyridinyl]urea (Example 31) was dissolved in 5 ml of MeOH/ $CH_2Cl_2$  (1:1) and 1M HCl (8 mL) in  $Et_2O$  solution was added. The solvents were removed *in vacuo* to afford the title salt as a yellow solid.

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**Example 33**

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**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-[3-(1-morpholinyl)propyl]amino]pyridinyl]urea**

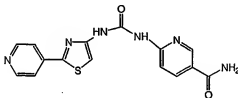
A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (200 mg, 0.86 mmol) and 2-amino-6-(3-(N-morpholinyl)propylamino)pyridine (300 mg, 1.27 mmol) in toluene (8 mL) was heated at 70°C for 1 h, and then at 80°C for 5 h. After the mixture was cooled to RT the solvent was removed *in vacuo* and the product was purified by chromatography on silica gel (1:10

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MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a light yellow solid: m.p. 215-217°C. MS m/z: 440 (M+1). Calc'd. for C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S - 439.541.

5

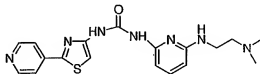
Example 34

10

[[[(2-(4-Pyridinyl)-4-thiazolylamino)carbonyl]amino]-2-pyridinyl-5-carboxamide

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 6-aminonicotinamide (200 mg, 1.45 mmol) in toluene (5 mL) was heated at 80°C for 6 h. After the mixture was cooled to RT the solvent was removed *in vacuo* and the crude product was purified by chromatography on silica gel (1:10 MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a light yellow solid: m.p. 255-257°C. MS m/z: 341 (M+1). Calc'd for C<sub>15</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>S - 340.37.

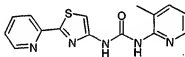
25

Example 35

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N'',N''-aminoethylamino)pyridinyl]urea

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A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (200 mg, 0.86 mmol) and 2-amino-6-(N,N-dimethylethylenediamino)pyridine (234 mg, 1.30 mmol) in toluene (10 mL) was heated at 70°C for 1 h, and then at  
5 80°C for 5 h. After the mixture was cooled to RT the solvent was removed in vacuo and the crude product was purified by chromatography on silica gel (1:10 MeOH(NH<sub>3</sub>)/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a light yellow solid: m.p. 210-212°C. MS m/z: 384 (M+1).  
10 Calc'd. for C<sub>18</sub>H<sub>22</sub>N<sub>6</sub>OS - 383.48.

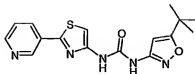
**Example 36**

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**N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(3-methylpyridinyl)urea**

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (500mg, 2.2 mmol) and 2-amino-3-methylpyridine (183mg, 6.6mmol) were heated in toluene (20 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et<sub>2</sub>O (3x10 mL). Recrystallization of the  
20 product from MeOH afforded the desired material: m.p. 235-237°C. MS m/z: 312 (M+H). Calc'd. for C<sub>15</sub>H<sub>11</sub>N<sub>5</sub>OS - 311.368.

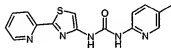
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**Example 37**

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**N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-[5-(1,1-dimethylethyl)-3-isoxazolyl]urea**

2-(3-Pyridinyl)-4-thiazolylcarbonylazide (300mg,  
 10 1.30 mmol) and 3-amino-5-(*tert*-butyl)isoxazole (491mg,  
 3.50 mmol) were heated in toluene (10 mL) at 95°C for  
 24 h. After cooling to RT, the solids were collected  
 by filtration and washed first with toluene (2x20 mL)  
 followed by cold EtOAc (3x10 mL) to give the product as  
 15 an off-white solid: m.p. 230-232° C. MS *m/z*: 344  
 (M+H). Calc'd. for C<sub>16</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S - 343.410.

**Example 38**

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**N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(5-methylpyridinyl)urea**

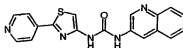
25 2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200mg,  
 0.87mmol) and 2-amino-5-methylpyridine (183mg, 1.7mmol)  
 were heated in toluene (15 mL) at 100°C for 12 h.  
 After cooling to RT, the solids were collected by  
 filtration and washed first with toluene (2x20mL)  
 30 followed by Et<sub>2</sub>O:EtOAc (3:1) (3x10 mL) to afford the

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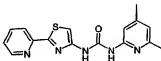
product as a tan solid: m.p. 228-230°C. MS  $m/z$ : 312 (M+H). Calc'd. for  $C_{15}H_{13}N_3OS$ -311.368.

**Example 39**

5

**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-3-quinolinylurea**

10 In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (53 mg, 0.229 mmol) and 3-aminoquinoline (36 mg, 260 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 348.5 (M+H). Calc. for  $C_{18}H_{13}N_3OS$  - 347.401.

**Example 40**

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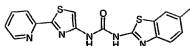
**N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(4,6-dimethylpyridinyl)urea**

25 2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200mg, 0.87mmol) and 2-amino-4,6-dimethylpyridine (210mg, 1.7mmol) were heated in toluene (15 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by  $Et_2O:EtOAc$  (3:1) (3 x 10 mL) to afford the product as a tan solid: m.p. 232-234°C. MS  $m/z$ : 326 (M+H). Calc'd. for  $C_{16}H_{15}N_3OS$  - 325.394.

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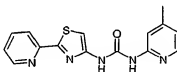
### Example 41



5 N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(6-methylbenzthiazolyl)urea

2-(2-Pyridinyl)-4-thiazolylcarbonylazine (200mg, 0.87mmol) and 2-amino-6-methylbenzothiazole (279mg, 1.7mmol) were heated in toluene (15 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by Et<sub>2</sub>O:EtOAc (3:1) (3 x 10 mL) to afford the product as a tan solid: m.p. 263-265°C. MS m/z: 312 (M+H). Calc'd. for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>OS<sub>2</sub> - 367.456.

### Example 42

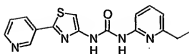


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N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(4-methylpyridinyl)urea

2-(2-Pyridinyl)-4-thiazolylcarbonylazine (200mg,  
25 0.87mmol) and 2-amino-4-methylpyridine (183mg, 1.7mmol)  
were heated in toluene (15 mL) at 100°C for 12 h.  
After cooling to RT, the solids were collected by  
filtration and washed first with toluene (2 x 20 mL)  
followed by Et<sub>2</sub>O:EtOAc (3:1) (3 x 10 mL) to afford the  
30 product as an off-white solid: m.p. 217-219°C. MS m/z:  
312 (M+H). Calc'd. for C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>S - 311.368.

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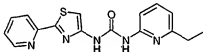
**Example 43**

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**N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea**

10 In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (186 mg, 0.804 mmol) and 2-amino-6-ethylpyridine (364 mg, 2.78 mmol) were heated in toluene (12 mL) to give the product as a pale yellow solid. MS  $m/z$ : 326.5 (M+H). Calc'd. for  $C_{16}H_{15}N_5OS$  - 325.395.

15

**Example 44**

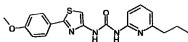
20

**N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea**

22 2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200mg, 0.87mmol) and 2-amino-6-ethylpyridine (318mg, 2.6mmol) were heated in toluene (10 mL) at 100°C for 14 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by Et<sub>2</sub>O (2 x 10mL) and cold EtOAc (3 x 5 mL) to give the product as a beige solid: m.p. 213-215°C.

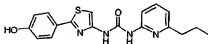
30 MS  $m/z$ : 326 (M+H). Calc'd. for  $C_{16}H_{15}N_5OS$  - 325.395.

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**Example 45**

5           **N-[2-(4-Methoxyphenyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea**

2-(4-Methoxyphenyl)-4-thiazolylcarbonylazide (280 mg, 1.1mmol) and 2-amino-6-n-propylpyridine (439 mg, 3.2 mmol) were heated in toluene (20 mL) at 100°C for 14 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et<sub>2</sub>O (2 x 10mL) and cold EtOAc (3 x5mL) to afford the product as an off-white solid. m.p. 223-225°C. MS m/z: 369 (M+H). Calc'd for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S - 368.461.

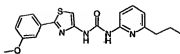
**Example 46**

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**N-[2-(4-Hydroxyphenyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea**

25           To a stirred solution of Example 45 (100mg, 0.271 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), boron tribromide was added dropwise at RT. The mixture was stirred for 8 h before adding H<sub>2</sub>O (10 ml) and the resulting solids were collected by filtration. This material was washed several times with H<sub>2</sub>O and then EtOAc followed by drying in vacuo to afford the desired product as a light yellow solid: m.p. 227-229°C. MS m/z: 355 (M+H). Calc'd for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S - 354.434.

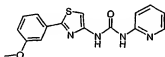
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Example 47

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**N-[2-(3-Methoxyphenyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea**

- 2-(3-Methoxyphenyl)-4-thiazolylcarbonylazide  
10 (1.0g, 3.8mmol) and 2-amino-6-n-propylpyridine (1.05g, 7.7mmol) were heated in toluene (40 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x40 mL) followed by cold EtOAc (3x20 mL) to afford the product as a white solid: m.p. 192-194°C. MS m/z: 369 (M+H).  
15 Calc'd for  $C_{19}H_{20}N_4O_2S$  - 368.461.

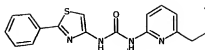
Example 48

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**N-[2-(3-Methoxyphenyl)-4-thiazolyl]-N'-2-pyridinylurea**

- 2-(3-Methoxyphenyl)-4-thiazolylcarbonylazide  
25 (1.0g, 3.8mmol) and 2-aminopyridine (0.72g, 7.7mmol) were heated in toluene (40 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x40 mL) followed by cold EtOAc (3x20 mL) to afford the product as a white solid: m.p. 201-203°C. MS m/z: 327 (M+H).  
30 Calc'd for  $C_{16}H_{14}N_4O_2S$  - 326.380.

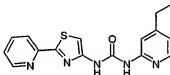
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**Example 49****5 N-[2-phenyl-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea**

In a manner similar to that described in Example 2, 2-phenyl-4-thiazolylcarbonylazide (150 mg, 0.652 mmol) and 2-amino-6-ethylpyridine (250 mg, 2.05 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 325.4 (M+H). Calc'd for  $C_{17}H_{16}N_4OS$  - 324.407.

**Example 50**

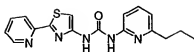
15

**20 N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea**

25

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200mg, 0.87mmol) and 2-amino-4-ethylpyridine (208mg, 1.7mmol) were heated in toluene (15 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by Et<sub>2</sub>O:EtOAc (3:1) (3 x 10 mL) to afford the product as a tan solid: m.p. 196-198°C. MS  $m/z$ : 326 (M+H). Calc'd. for  $C_{18}H_{15}N_5OS$  - 325.395.

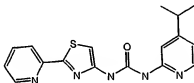
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**Example 51**

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**N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea**

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200mg,  
10 0.87mmol) and 2-amino-6-(n-propyl)pyridine (350mg,  
2.6mmol) were heated in toluene (10mL) at 100°C for 14  
h. After cooling to RT, the solids were collected by  
filtration and washed first with toluene (2 x 20 mL)  
followed by Et<sub>2</sub>O (2 x 10mL) and cold EtOAc (3 x 5 mL)  
15 to give the product as a grayish solid: m.p. 210-212°C.  
MS m/z: 340 (M+H). Calc'd. for C<sub>17</sub>H<sub>17</sub>N<sub>5</sub>O - 339.422.

**Example 52**

20

**N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-[4-(1-methylethyl)pyridinyl]urea**

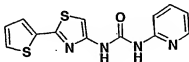
25 2-(2-Pyridinyl)-4-thiazolylcarbonylazide (300mg,  
1.3mmol) and 2-amino-4-isopropylpyridine (500mg,  
3.6mmol) were heated in 10 mL toluene at 100°C for 12  
h. After cooling to RT, the solvent was removed by  
rotary evaporation and the crude oil purified by  
30 column chromatography with hexane:EtOAc (7:3) as

- 182 -

eluant to give the urea as a light yellow solid. MS  $m/z$ : 340 (M+H). Calc'd for  $C_{17}H_{11}N_4OS$  - 339.42.

**Example 53**

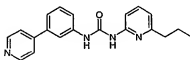
5

**N-[2-(2-Thienyl)-4-thiazolyl]-N'-2-(pyridinyl)urea**

- 10        2-(2-Thienyl)-4-thiazolylcarbonylazide (200mg, 0.85mmol) and 2-aminopyridine (154mg, 1.62mmol) were heated in 20 mL toluene at 100°C for 16 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by  
15        Et<sub>2</sub>O: EtOAc (3:1) (3 x 10 mL) to afford the urea as an off-white solid. MS  $m/z$ : 303 (M+H). Calc'd for  $C_{13}H_{10}N_4OS_2$  - 302.38.

**Example 54**

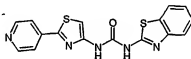
20

**N-[3-(4-Pyridinyl)phenyl]-N'-2-(6-propylpyridinyl)urea**

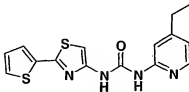
- 25        To a suspended anhydrous solution of 4-pyridylaniline (180 mg, 1.06 mmol) in dry toluene (8 mL) was added phosgene (0.73 mL, 1.38 mmol, 20% in toluene) followed by N,N-diisopropylethylamine (0.37 mL, 2.11 mmol) under an atmosphere of argon. After  
30        stirring for 0.5 h at RT, 2-amino-6-(n-propyl)pyridine (144 mg, 1.06 mmol) in dry toluene (3 mL) was added dropwise into the reaction mixture. The resulting

- 183 -

mixture was stirred at RT for 18 h. The organic solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel using 5% methanol/dichloromethane as eluant to obtain the final urea as white solid: m.p. 195-198°C. MS  $m/z$ : 333.4 (M+H). Calc'd. for  $C_{22}H_{18}N_4O$  - 332.405.

**Example 55****N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-benzthiazolylurea**

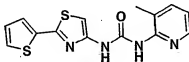
In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (52 mg, 0.225 mmol) and 2-aminobenzothiazole (41 mg, 0.273 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS  $m/z$ : 354.4 (M+H). Calc'd. for  $C_{18}H_{11}N_5OS_2$  - 353.427.

**Example 56****N-[2-(2-Thienyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea**

2-(2-Thienyl)-4-thiazolylcarbonylazide (500mg, 2.1mmol) and 2-amino-4-ethylpyridine (512mg, 4.2mmol)

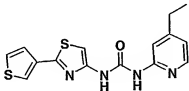
- 184 -

were heated in 15 mL toluene at 100°C for 16 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by Et<sub>2</sub>O:EtOAc (3:1) (3 x 10 mL) to afford the urea as an off-white solid. MS m/z: 331 (M+H). Calc'd for C<sub>13</sub>H<sub>11</sub>N<sub>4</sub>OS<sub>2</sub> - 330.435.

**Example 57**

**N-[2-(2-Thienyl)-4-thiazolyl]-N'-2-(3-methylpyridinyl)urea**

2-(2-Thienyl)-4-thiazolylcarbonylazide (500mg, 2.1mmol) and 2-amino-3-methylpyridine (449mg, 4.2mmol) were heated in 15 mL toluene at 100°C for 16 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et<sub>2</sub>O:EtOAc (3:1) (3x10 mL) to afford the urea as an off-white solid. MS m/z: 317 (M+H). Calc'd for C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>OS<sub>2</sub> - 316.408.

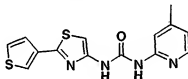
**Example 58**

**N-[2-(3-Thienyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea**

- 185 -

- 2-(3-Thienyl)-4-thiazolylcarbonylazide (200mg, 0.85mmol) and 2-amino-4-ethylpyridine (310mg, 2.54 mmol) were heated in 10 mL toluene at 100°C for 16 h. After cooling to RT, the solids were collected by
- 5 filtration and washed first with toluene (2x20 mL) followed by Et<sub>2</sub>O:EtOAc (3:1; (3x10 mL) to afford the product as an off-white solid. MS *m/z*: 331 (M+H). Calc'd for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>OS<sub>2</sub> - 330.435.

10

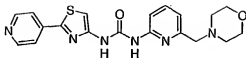
Example 59

**N-[2-(3-Thienyl)-4-thiazolyl]-N'-2-(4-methylpyridinyl)urea**

15

- 2-(3-Thienyl)-4-thiazolylcarbonylazide (200mg, 0.85mmol) and 2-amino-4-methylpyridine (272mg, 2.54mmol) were heated in 10 mL toluene at 100°C for 16 h. After cooling to RT, the solids were collected by
- 20 filtration and washed first with toluene (2x20mL) followed by Et<sub>2</sub>O: EtOAc (3:1) (3x10mL) to afford the product as an off-white solid. MS *m/z*: 317 (M+H). Calc'd for C<sub>15</sub>H<sub>13</sub>N<sub>4</sub>OS<sub>2</sub> - 316.408.

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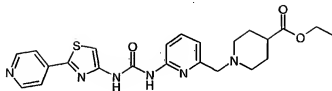
Example 60

5           N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-  
            morpholinylmethyl)pyridinyl]urea

          2-(4-Pyridinyl)-4-thiazolcarbonylazide (100 mg,  
          0.43 mmol) in dry toluene (10 mL) was heated to 85°C  
10   under N<sub>2</sub> and maintained at for 5 min. A solution of 6-  
          morpholin-4-ylmethyl-pyridin-2-ylamine (101 mg, 0.52  
          mmol) in dry toluene (2 mL) was added dropwise via  
          syringe and the resulting mixture was heated at 100°C  
          for 12 h. After cooling to RT, a precipitate formed  
15   and was collected, rinsing with hexane to give a white  
          solid. MS *m/z*: 397.3 (M+H). Calc'd for C<sub>19</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>S:  
          396.14.

          The following compounds were prepared from the  
20   corresponding amines in a manner similar to that  
          described above for Example 60:

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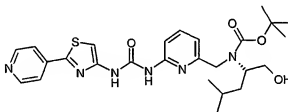
Example 61

5

**Ethyl 1-{6-[3-(2-(pyridin-4-yl)thiazol-4-yl)ureido]-  
pyridin-2-ylmethyl}-piperidine-4-carboxylate**

2-(4-Pyridinyl)-4-thiazolcarbonylazide (182 mg,  
10 0.87 mmol) heated with ethyl 1-(6-aminopyridin-2-  
ylmethyl)-piperidine-4-carboxylate (230 mg, 0.87 mmol)  
in dry toluene (15 mL) gave the final urea. MS m/z:  
466.9 (M+H). Calc'd. for  $C_{23}H_{26}N_6O_3S$  - 466.50.

15

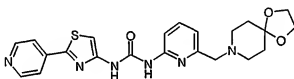
Example 62

**tert-Butyl (1-(hydroxymethyl)-3-methyl-butyl)-{6-[3-(2-  
20 pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-  
carbamate**

2-(4-Pyridinyl)-4-thiazolcarbonylazide (343 mg,  
1.48 mmol) was heated with 2-amino-6-[N'-tert-

- 188 -

butoxycarbonyl-N'-2-(1-hydroxy-4-methyl)pentylamino]methylpyridine (480 mg, 1.48 mmol) in dry toluene (20 mL) to yield the final compound as pale yellow solid. MS  $m/z$ : 527.6 (M+H). Calc'd. for  $C_{26}H_{34}N_6O_4S$  - 526.66.

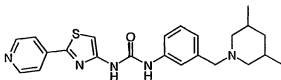
Example 63

10

1-[6-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (420 mg, 2.01 mmol) was heated with 2-amino-6-(4-ethoxyacetal)piperidinylmethyl pyridine ( 500 mg, 2.01 mmol) in dry toluene (30 mL) to yield the final compound as yellow solid. MS  $m/z$ : 452.9 (M+H). Calc'd. for  $C_{22}H_{24}N_6O_3S$  - 452.23.

20

Example 64

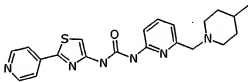
25 1-[6-(3,5-Dimethylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-ylthiazol-4-yl)urea

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2-(4-Pyridinyl)-4-thiazolcarbonylazide (200 mg, 0.867 mmol) was heated with 2-amino-6-(3,5-dimethyl)piperidinyl-methylpyridine (190 mg, 0.867 mmol) in dry toluene (20 mL) to yield the final compound as yellow solid. MS  $m/z$ : 423.2 (M+H). Calc'd. for  $C_{22}H_{26}N_6OS$  - 422.0.

Example 65

10



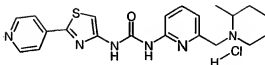
1-[6-(4-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

15

2-(4-Pyridinyl)-4-thiazolcarbonylazide (348 mg, 1.51 mmol) was heated with 2-amino-6-(4-methyl)piperidinyl-methylpyridine (310 mg, 1.51 mmol) in dry toluene (20 mL) to yield the final compound as pale yellow solid. MS  $m/z$ : 409.5 (M+H). Calc'd. for  $C_{21}H_{24}N_6OS$  - 408.52.

20

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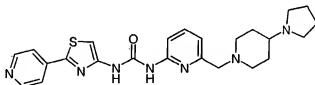
Example 66

5

1-[6-(2-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (101 mg, 0.44 mmol) was heated with 2-amino-6-(2-methyl)piperidinylmethyl pyridine (90 mg, 0.44 mmol) in dry toluene (15 mL) to yield the final compound as pale yellow solid. MS  $m/z$ : 409.6 (M+H). Calc'd. for  $C_{21}H_{24}N_6OS$  - 408.52.

15

Example 67

1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-pyridin-2-yl]-urea

2-(4-pyridinyl)-4-thiazolcarbonylazide (293 mg, 1.43 mmol) was heated with 2-amino-6-[4-(1-pyrrolidinyl)piperidinylmethyl] pyridine (330 mg, 1.43 mmol) in dry toluene (20 mL) to yield the final

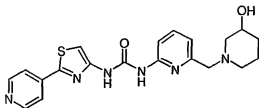
25

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compound as pale yellow solid. MS  $m/z$ : 464.2 (M+H).  
Calc'd. for  $C_{24}H_{29}N_7OS$  - 463.

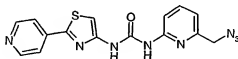
**Example 68**

5



**1-[6-(3-Hydroxy-piperidin-1-ylmethyl)-pyridin-2-yl]-3-  
(2-pyridin-4-yl-thiazol-4-yl)-urea**

10            2-(4-Pyridinyl)-4-thiazolcarbonylazide (312 mg,  
1.35 mmol) was heated with 2-amino-6-(3-hydroxy)-  
piperidinylmethyl pyridine (280 mg, 1.35 mmol) in dry  
toluene (20 mL) to yield the final compound as yellow  
solid. MS  $m/z$ : 410.9 (M+H). Calc'd. for  $C_{20}H_{22}N_6O_2S$  -  
15 410.5.

**Example 69**

20

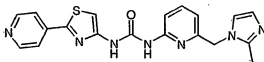
**N-(6-azidomethyl-2-pyridyl)-N'-[2-(4-pyridinyl)-4-  
thiazolyl]urea**

25            2-(4-Pyridinyl)-4-thiazolcarbonylazide (400 mg,  
1.73 mmol) was heated with 2-amino-6-azidomethyl-

- 192 -

pyridine (258 mg, 1.73 mmol) in dry toluene (15 mL) to yield the final compound as yellow solid. MS  $m/z$ : 353.4 (M+H). Calc'd. for  $C_{15}H_{12}N_8OS$  - 352.38.

5

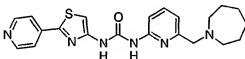
Example 70

10

1-[6-(2-Methyl-imidazol-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (110 mg, 0.48 mmol) was heated with 2-amino-6-[2-methylimidazol-1-yl]methyl-pyridine (90 mg, 0.48 mmol) in dry toluene (15 mL) to yield the final compound as white solid. MS  $m/z$ : 392.4 (M+H). Calc'd. for  $C_{19}H_{17}N_7OS$  - 391.45.

15

Example 71

20

1-(6-Azepan-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

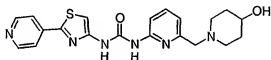
2-(4-Pyridinyl)-4-thiazolcarbonylazide (150 mg, 0.65 mmol) and 2-amino-6-azaperhydroepinylmethylpyridine (147 mg, 0.71 mmol) in

25

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dry toluene (15 mL) were heated at 100°C for 12 h to give a pale yellow solid. MS  $m/z$ : 409.1 (M+H).  
Calc'd for  $C_{21}H_{24}N_6OS$  - 408.52.

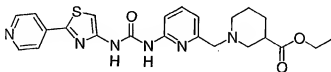
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Example 72

10 1-[6-(4-Hydroxypiperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (265 mg, 1.27 mmol) and 2-amino-6-(4-hydroxy)piperidyl-methylpyridine (220 mg, 1.06 mmol) in dry toluene (15 mL) were heated at 100°C for 12 h to give a pale yellow solid which was recrystallized from  $CHCl_3$ /MeOH/hexane (94:2:1) to give a white solid. MS  $m/z$ : 410.9 (M+H).  
Calc'd for  $C_{20}H_{22}N_6O_2S$  - 410.50.

20

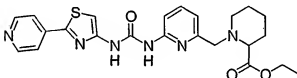
Example 73

25 Ethyl 1-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl)piperidine-3-carboxylate

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2-(4-Pyridinyl)-4-thiazolcarbonylazide (150 mg, 0.65 mmol) and 2-amino-ethyl(6-piperidylmethyl-pyridinyl)-3-carboxylate (170 mg, 0.65 mmol) in dry toluene (15 mL) were heated at 100°C for 12 h to give a pale yellow solid which was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5) to give a white solid. MS m/z: 467.1 (M+H). Calc'd for C<sub>23</sub>H<sub>26</sub>N<sub>6</sub>O<sub>3</sub>S - 466.56.

10

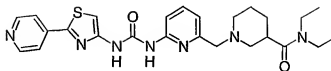
**Example 74**

15 **Ethyl 1-[6-[3-(2-(pyridin-4-yl)thiazol-4-yl)ureido]-pyridin-2-ylmethyl]piperidine-2-carboxylate**

2-(4-Pyridinyl)-4-thiazolcarbonylazide (483 mg, 2.09 mmol) and ethyl 2-amino-(6-piperidylmethyl-pyridinyl)-2-carboxylate (550 mg, 2.09 mmol) in dry toluene (20 mL) were heated at 100°C for 8 h to give a pale yellow solid which was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5) to give a white solid. MS m/z: 466.9 (M+H). Calc'd for C<sub>23</sub>H<sub>26</sub>N<sub>6</sub>O<sub>3</sub>S - 466.56.

25

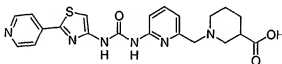
- 195 -

Example 75

5

N,N-Diethyl 1-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-  
ureido]pyridin-2-ylmethyl)piperidine-3-carboxamide

2-(4-Pyridinyl)-4-thiazolcarbonylazide (320 mg,  
10 1.38 mmol) and 2-amino-6-[(N',N''-diethylcarbamoyl)-  
piperidylmethyl]-3-carboxamide (400 mg, 1.38 mmol) in  
dry toluene (25 mL) were heated at 100°C for 12 h to  
give a pale yellow solid which was purified by  
chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5) to  
15 give a white solid. MS m/z: 494.1 (M+H). Calc'd for  
C<sub>25</sub>H<sub>31</sub>N<sub>7</sub>O<sub>2</sub>S - 493.63.

Example 76

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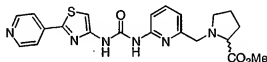
1-(6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-  
2-ylmethyl)-piperidine-3-carboxylic acid

25 2-(4-Pyridinyl)-4-thiazolcarbonylazide (196 mg,  
0.85 mmol) and 2-amino-6-(piperidylmethylpyridinyl)-3-  
carboxylate (200 mg, 0.85 mmol) in dry toluene (10 mL)

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were heated at 100°C for 8 h to give a pale yellow solid which was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95 :5) to give a white solid. MS *m/z*: 437.9 (M+H). Calc'd for C<sub>21</sub>H<sub>22</sub>N<sub>6</sub>O<sub>3</sub>S - 438.51.

5

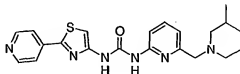
Example 77

10      **Methyl 1-([6-([3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-yl)methyl]-pyrrolidine-2-carboxylate**

2-(4-Pyridinyl)-4-thiazolcarbonylazide (104 mg, 0.45 mmol) and 2-amino-6-(2-methoxycarbonyl)-

15      pyrrolidinyl-methylpyridine (105 mg, 0.45 mmol) in dry toluene (10 mL) were heated at 100°C for 12 h to give a pale yellow solid which was purified by chromatography on silica gel (CHCl<sub>3</sub>/MeOH, 99:5) to give a white solid. MS *m/z*: 438.7 (M+H). Calc'd for C<sub>21</sub>H<sub>22</sub>N<sub>6</sub>O<sub>3</sub>S - 438.51.

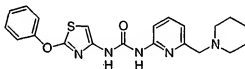
20

Example 78

25      **1-([6-([3-(3-Methyl-piperidin-1-yl)methyl]-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

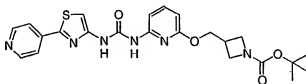
- 197 -

2-(4-Pyridinyl)-4-thiazolcarbonylazide (259 mg, 1.12 mmol) and 2-amino-6-(3-methyl)piperidinylmethylpyridine (230 mg, 1.12 mmol) in dry toluene (15 mL) were heated at 100°C for 12 h to give a pale yellow solid which was purified by chromatography on silica gel (CHCl<sub>3</sub>/ MeOH, 99:5) to give a white solid. MS m/z: 408.8 (M+H). Calc'd for C<sub>21</sub>H<sub>24</sub>N<sub>6</sub>OS - 408.53.

Example 79

1-(2-Phenoxy-thiazol-4-yl)-3-(6-piperidin-1-ylmethylpyridin-2-yl)-urea

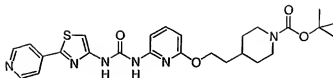
MS m/z: 410 (M+H). Calc'd for C<sub>21</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub>S: 409.16.

Example 80

tert Butyl 3-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxymethyl}-azetidine-1-carboxylate

MS m/z: 483 (M+H). Calc'd for C<sub>23</sub>H<sub>26</sub>N<sub>6</sub>O<sub>4</sub>S: 482.17.

- 198 -

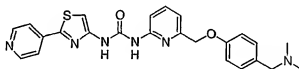
Example 81

5

tert Butyl 4-(2-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-  
ureido]pyridin-2-yloxy}ethyl)piperidine-1-carboxylate

MS  $m/z$ : 525 (M+H). Calc'd for  $C_{26}H_{32}N_6O_4S$ : 524.22

10

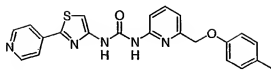
Example 82

15 1-[6-(4-Dimethylaminomethyl-phenoxy)methyl]-pyridin-2-  
yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

MS  $m/z$ : 461 (M+H). Calc'd for  $C_{24}H_{24}N_6O_2S$ : 460.17.

20

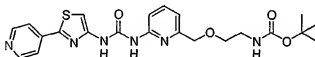
- 199 -

Example 83

5           1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-(4-methylphenyl)oxymethylpyridin-2-yl)urea

MS  $m/z$ : 416 (M-H). Calc'd for  $C_{22}H_{19}N_5O_2S$ : 417.13.

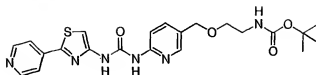
10

Example 84

15           tert Butyl (2-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-ylmethoxy}ethyl)carbamate

MS  $m/z$ : 471 (M+H). Calc'd for  $C_{22}H_{26}N_6O_4S$ : 470.17.

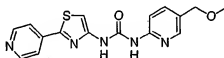
- 200 -

Example 85

5        **tert Butyl (2-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-  
ureido]pyridin-3-ylmethoxy}ethyl)carbamate**

MS  $m/z$ : 471 (M+H). Calc'd for  $C_{22}H_{26}N_6O_4S$ : 470.17.

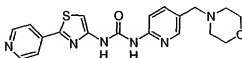
10

Example 86

15        **1-(5-Methoxymethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-  
thiazol-4-yl)-urea**

MS  $m/z$ : 342 (M+H). Calc'd for  $C_{16}H_{15}N_5O_2S$ : 341.09.

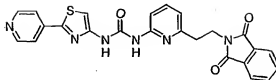
20

Example 87

25        **1-(5-Morpholin-4-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-  
yl-thiazol-4-yl)urea**

MS  $m/z$ : 397 (M+H). Calc'd for  $C_{19}H_{20}N_6O_2S$ : 396.14.

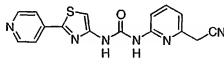
- 201 -

Example 88

5

**1-(6-[2-phthalimidylethyl]pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

Prepared in a manner similar to that described in  
10 Example 60 from 3-(4-pyridyl)-thiazole acyl-azide (103 mg, 0.56 mmol) and 2-amino-6-ethylphthalamidylypyridine (150 mg, 0.56 mmol) in toluene (10 mL). Concentrated in vacuo to afford a yellow solid which was treated with EtOH (10 mL) and filtered to give the title  
15 compound as a yellow solid. MS m/z: 470.9 (M+H).  
Calc'd for C<sub>24</sub>H<sub>18</sub>N<sub>6</sub>O<sub>3</sub>S: 470.12.

Example 89

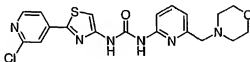
20

**1-(6-Cyanomethylpyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

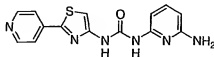
25 Prepared in a manner similar to that described in Example 60 from 2-amino-6-methylnitrile-pyridine (0.32 g, 2.4 mmol) and 3-(4-pyridyl)-4-thiazole acylazide

- 202 -

(0.51 g, 2.2 mmol). After 1.5 h, yellow solid precipitated out of toluene solution. The mixture was cooled to RT and the solid filtered. Purified by silica flash chromatography (3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a white solid. MS m/z: 337.1 (M+H). Calc'd for C<sub>16</sub>H<sub>12</sub>N<sub>6</sub>OS: 336.08.

**Example 90****1-[2-(2-Chloropyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea**

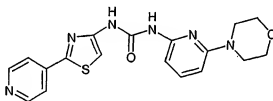
Prepared in a manner similar to that described in Example 60 from 3-(4-pyridyl)-4-thiazole acyl azide (0.51 g, 1.9 mmol) and 2-amino-6-methylmorpholino-pyridine (0.42g, 2.2 mmol) in toluene (50 mL). After 3 h, the reaction mixture was cooled to RT and filtered to afford the title compound as a light purple solid. MS m/z: 431.0 (M+H). Calc'd for C<sub>19</sub>H<sub>19</sub>ClN<sub>6</sub>O<sub>2</sub>S: 430.10.

**Example 91****1-(6-Aminopyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

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Prepared in a manner similar to that described in Example 60 from 3-(4-pyridyl)-4-thiazole-acyl azide (148 mg, 0.64 mmol) and 2,6-diaminopyridine (77 mg, 0.70 mmol, Aldrich) in toluene (10 mL). After 2 h, a yellow precipitate formed. The reaction mixture was cooled and filtered to afford the title compound as a yellow solid. MS m/z: 180 (M+H). Calc'd for  $C_{14}H_{12}N_6OS$ : 312.08.

10

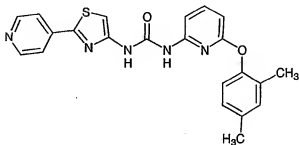
**Example 92**

15     1-(6-Morpholin-4-yl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 383.4 (M+H). Calc'd for  $C_{18}H_{18}N_6O_2S$ : 382.12.

20

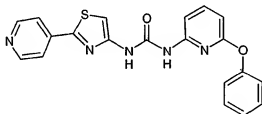
- 204 -

Example 93

5    1-[6-(2,4-Dimethylphenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 418.5 (M+H). Calc'd for C<sub>22</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub>S: 417.13.

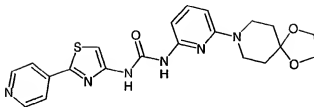
10

Example 94

15    1-(6-Phenoxypyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

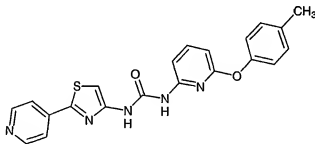
EI-MS m/z 390.4 (M+H). Calc'd for C<sub>20</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>S: 389.09.3

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Example 95

5     1-[6-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

Prepared in a manner similar to that described in Example 60 using 2-(4-pyridinyl)-4-thiazolcarbonylazine and the requisite 2-aminopyridine. EI-MS m/z 439.5 (M+H). Calc'd for C<sub>21</sub>H<sub>22</sub>N<sub>6</sub>O<sub>3</sub>S: 438.15.

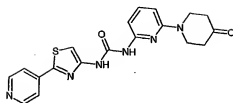
Example 96

15

1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-p-tolyloxy-pyridin-2-yl)-urea

20     EI-MS m/z 404.4 (M+H). Calc'd for C<sub>21</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S: 403.11.

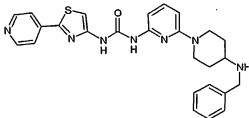
- 206 -

Example 97

5      1-(4-Oxo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-  
yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 395.4 (M+H). Calc'd for C<sub>19</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub>S: 394.12.

10

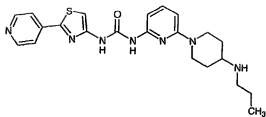
Example 98

15      1-(4-Benzylamino-3,4,5,6-tetrahydro-2H-  
[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-  
yl)-urea

EI-MS m/z 486.7 (M+H). Calc'd for C<sub>26</sub>H<sub>27</sub>N<sub>7</sub>OS: 485.20.

20

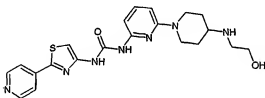
- 207 -

Example 99

5           1-(4-Propylamino-3,4,5,6-tetrahydro-2H-  
[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-  
yl)-urea

EI-MS m/z 438.6 (M+H). Calc'd for C<sub>22</sub>H<sub>27</sub>N<sub>7</sub>OS: 437.20.

10

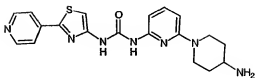
Example 100

15           1-[4-(2-Hydroxy-ethylamino)-3,4,5,6-tetrahydro-2H-  
[1,2']bipyridinyl-6'-yl]-3-(2-pyridin-4-yl-thiazol-4-  
yl)-urea

EI-MS m/z 440.5 (M+H). Calc'd for C<sub>21</sub>H<sub>25</sub>N<sub>7</sub>O<sub>2</sub>S: 439.18.

20

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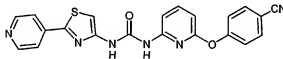
Example 101

5

1-(4-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-  
yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 396.6 (M+H). Calc'd for C<sub>19</sub>H<sub>21</sub>N<sub>7</sub>OS: 395.15.

10

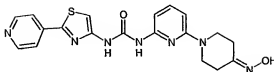
Example 102

15 1-[6-(4-Cyanophenoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-  
thiazol-4-yl)urea

EI-MS m/z 415.5 (M+H). Calc'd for C<sub>21</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>S: 414.09.

20

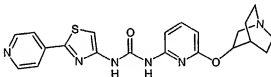
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Example 103

5           1-(4-Hydroxyimino-3,4,5,6-tetrahydro-2H-  
[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-  
yl)-urea

EI-MS m/z 410.4 (M+H). Calc'd for C<sub>19</sub>H<sub>19</sub>N<sub>7</sub>O<sub>2</sub>S: 409.13.

10

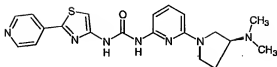
Example 104

15       1-[6-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-pyridin-2-yl]-3-  
(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 423.6 (M+H). Calc'd for C<sub>21</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub>S: 422.15.

20

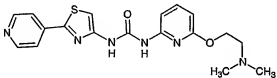
- 210 -

Example 105

5    1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-pyridin-2-yl]-3-  
       (2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z    410.5 (M+H).    Calc'd for C<sub>20</sub>H<sub>23</sub>N<sub>7</sub>OS: 409.17.

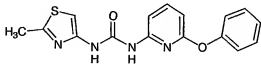
10

Example 106

15    1-[6-(2-Dimethylamino-ethoxy)-pyridin-2-yl]-3-(2-  
       pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z    385.5 (M+H).    Calc'd for C<sub>18</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>S: 384.14.

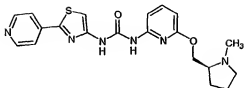
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Example 107

25    1-(2-Methylthiazol-4-yl)-3-(6-phenoxy-pyridin-2-yl)urea

EI-MS m/z    327.4 (M+H).    Calc'd for C<sub>16</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>S: 326.08.

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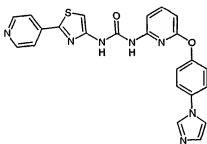
Example 108

5

1-[6-(1-Methylpyrrolidin-2-ylmethoxy)pyridin-2-yl]-3-  
(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 411.4 (M+H). Calc'd for  $C_{20}H_{22}N_6O_2S$ : 410.15.

10

Example 109

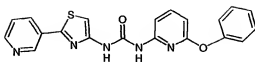
15

1-[6-(4-Imidazol-1-yl-phenoxy)-pyridin-2-yl]-3-(2-  
pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 456.6 (M+H). Calc'd for  $C_{23}H_{17}N_7O_2S$ : 455.12.

20

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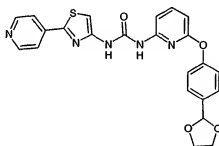
Example 110

5

1-(6-Phenoxy pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)urea

EI-MS m/z 390.5 (M+H). Calc'd for  $C_{20}H_{15}N_5O_2S$ : 389.09.

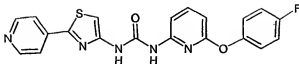
10

Example 111

15 1-[6-(4-[1,3]Dioxolan-2-yl-phenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 462.5 (M+H). Calc'd for  $C_{23}H_{19}N_5O_4S$ : 461.12.

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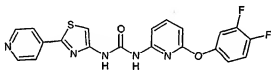
Example 112

5

1-[6-(4-Fluorophenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-  
thiazol-4-yl)urea

EI-MS m/z 408.5 (M+H). Calc'd for C<sub>20</sub>H<sub>14</sub>FN<sub>5</sub>O<sub>2</sub>S: 407.09.

10

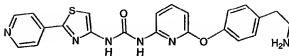
Example 113

15 1-[6-(3,4-Difluorophenoxy)pyridin-2-yl]-3-(2-pyridin-4-  
yl-thiazol-4-yl)urea

EI-MS m/z 426.5 (M+H). Calc'd for C<sub>20</sub>H<sub>13</sub>F<sub>2</sub>N<sub>5</sub>O<sub>2</sub>S: 425.08.

20

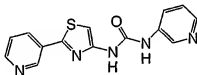
- 214 -

Example 114

5        1-{6-[4-(2-Aminoethyl)phenoxy]pyridin-2-yl}-3-(2-  
pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 433.5 (M+H). Calc'd for C<sub>22</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>S: 432.14.

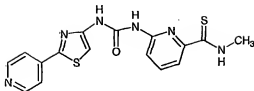
10

Example 115

15        1-Pyridin-3-yl-3-(2-pyridin-3-yl-thiazol-4-yl)-urea

EI-MS m/z 396.6 (M+H). Calc'd for C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>OS: 297.07.

- 215 -

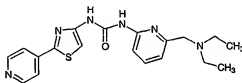
Example 116

5

6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridine-2-carbothioic acid methylamide

EI-MS m/z 371.5 (M+H). Calc'd for  $C_{16}H_{14}N_6OS_2$ : 370.07.

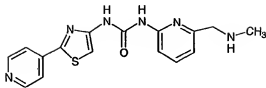
10

Example 117

15 1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 383.5 (M+H). Calc'd for  $C_{19}H_{22}N_6OS$ : 382.16.

- 216 -

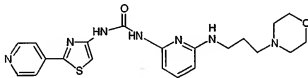
Example 118

5

1-(6-Methylaminomethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 341.4 (M+H). Calc'd for C<sub>16</sub>H<sub>16</sub>N<sub>6</sub>OS: 340.11.

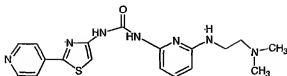
10

Example 119

15 1-[6-(3-Morpholin-4-yl-propylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 440.4 (M+H). Calc'd for C<sub>21</sub>H<sub>25</sub>N<sub>7</sub>O<sub>2</sub>S: 439.18.

- 217 -

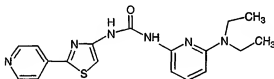
Example 120

5

1-[6-(2-Dimethylamino-ethylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 384.5 (M+H). Calc'd for C<sub>18</sub>H<sub>21</sub>N<sub>7</sub>OS: 383.15.

10

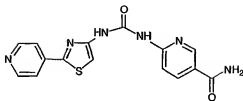
Example 121

15

1-(6-Diethylamino-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 369.3 (M+H). Calc'd for C<sub>18</sub>H<sub>20</sub>N<sub>6</sub>OS: 368.14.

- 218 -

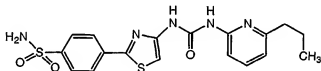
Example 122

5

6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]nicotinamide

EI-MS m/z 341.3 (M+H). Calc'd for C<sub>15</sub>H<sub>12</sub>N<sub>6</sub>O<sub>2</sub>S: 340.07.

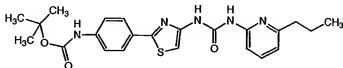
10

Example 123

15

4-{4-[3-(6-Propylpyridin-2-yl)ureido]thiazol-2-yl}-  
benzenesulfonamideEI-MS m/z 418.5 (M+H). Calc'd for C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>O<sub>3</sub>S<sub>2</sub>: 417.09.

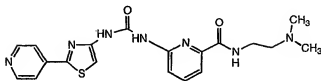
20

Example 124tert Butyl (4-{4-[3-(6-Propylpyridin-2-yl)ureido]-  
thiazol-2-yl}phenyl)carbamate

- 219 -

EI-MS m/z 454.6 (M+H). Calc'd for  $C_{23}H_{27}N_5O_3S$ : 453.18.Example 125

5

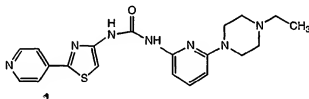


2-Dimethylaminoethyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridine-2-carboxamide

10

EI-MS m/z 412.5 (M+H). Calc'd for  $C_{19}H_{21}N_7O_2S$ : 411.15.Example 126

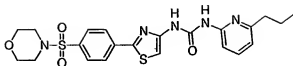
15



1-[6-(4-Ethylpiperazin-1-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

20 EI-MS m/z 410.6 (M+H). Calc'd for  $C_{20}H_{23}N_7OS$ : 409.17.

- 220 -

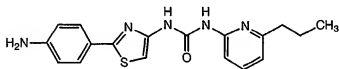
Example 127

5

1-[2-[4-(4-Morpholinylsulfonyl)phenyl]thiazol-4-yl]-3-  
(6-propyl-pyridin-2-yl)urea

EI-MS m/z 488.7 (M+H). Calc'd for  $C_{22}H_{25}N_5O_4S_2$ : 487.13.

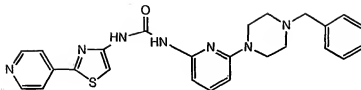
10

Example 128

15 1-[2-(4-Aminophenyl)thiazol-4-yl]-3-(6-propylpyridin-2-  
yl)urea

EI-MS m/z 354.4 (M+H). Calc'd for  $C_{18}H_{19}N_5OS$ : 353.13.

- 221 -

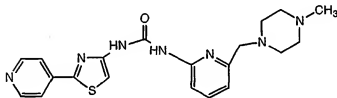
Example 129

5

1-[6-(4-Benzylpiperazin-1-yl)pyridin-2-yl]-3-(2-  
pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 472.5 (M+H). Calc'd for C<sub>25</sub>H<sub>25</sub>N<sub>7</sub>OS: 471.18.

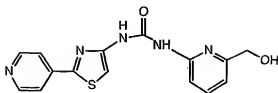
10

Example 130

15 1-[6-(4-Methylpiperazin-1-ylmethyl)-pyridin-2-yl]-3-  
(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 410.5 (M+H). Calc'd for C<sub>20</sub>H<sub>23</sub>N<sub>7</sub>OS: 409.17.

- 222 -

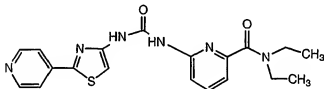
Example 131

5

1-(6-Hydroxymethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 328.4 (M+H). Calc'd for C<sub>15</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>S: 327.08.

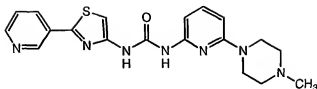
10

Example 132

15 Diethyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridine-2-carboxamide

EI-MS m/z 397.6 (M+H). Calc'd for C<sub>19</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>S: 396.14.

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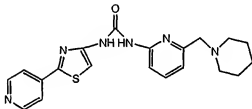
Example 133

5

1-[6-(4-Methylpiperazin-1-yl)pyridin-2-yl]-3-(2-  
pyridin-3-yl-thiazol-4-yl)urea

EI-MS m/z 396.5 (M+H). Calc'd for C<sub>19</sub>H<sub>21</sub>N<sub>7</sub>OS: 395.15.

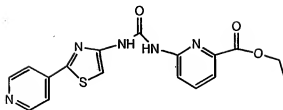
10

Example 134

15 1-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-  
yl-thiazol-4-yl)-urea

EI-MS m/z 395.6 (M+H). Calc'd for C<sub>20</sub>H<sub>22</sub>N<sub>6</sub>OS: 394.16.

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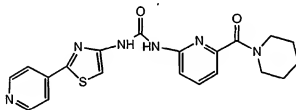
Example 135

5

6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridine-2-  
carboxylic acid ethyl ester

EI-MS m/z 370.4 (M+H). Calc'd for  $C_{17}H_{15}N_5O_3S$ : 369.09.

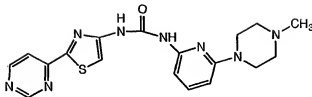
10

Example 136

15 1-[6-(Piperidine-1-carbonyl)pyridin-2-yl]-3-(2-pyridin-  
4-yl-thiazol-4-yl)urea

EI-MS m/z 409.5 (M+H). Calc'd for  $C_{20}H_{20}N_6O_2S$ : 408.14.

- 225 -

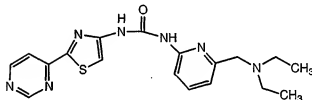
Example 137

5

1-[6-(4-Methylpiperazin-1-yl)pyridin-2-yl]-3-(2-  
pyrimidin-4-yl-thiazol-4-yl)urea

EI-MS m/z 397.5 (M+H). Calc'd for  $C_{18}H_{20}N_8OS$ : 396.15.

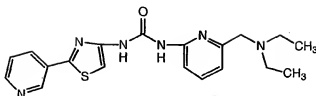
10

Example 138

15 1-(6-(Diethylaminomethyl-pyridin-2-yl)-3-(2-pyrimidin-4-  
yl-thiazol-4-yl)urea

EI-MS m/z 384.6 (M+H). Calc'd for  $C_{18}H_{21}N_7OS$ : 383.15.

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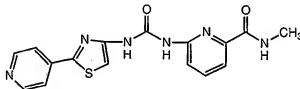
Example 139

5

1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)urea

EI-MS m/z 383.5 (M+H). Calc'd for  $C_{19}H_{22}N_6OS$ : 382.16.

10

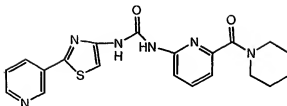
Example 140

15

Methyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridine-2-carboxamide

EI-MS m/z 355.3 (M+H). Calc'd for  $C_{16}H_{14}N_6O_2S$ : 354.09.

- 227 -

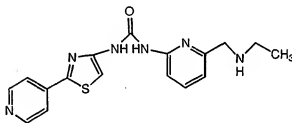
Example 141

5

1-[6-(Piperidine-1-carbonyl)pyridin-2-yl]-3-(2-pyridin-  
3-yl-thiazol-4-yl)urea

EI-MS m/z 409.5 (M+H). Calc'd for C<sub>20</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>S: 408.14.

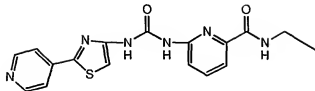
10

Example 142

15 1-(6-Ethylaminomethylpyridin-2-yl)-3-(2-pyridin-4-yl-  
thiazol-4-yl)urea

EI-MS m/z 355.5 (M+H). Calc'd for C<sub>17</sub>H<sub>18</sub>N<sub>6</sub>OS: 354.13.

- 228 -

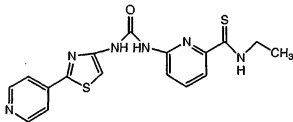
Example 143

5

**Ethyl 6-[3-(2-Pyridin-4-yl-thiazol-4-yl)ureido]pyridine-2-carboxamide**

EI-MS m/z 369.4 (M+H). Calc'd for  $C_{17}H_{16}N_6O_2S$ : 368.11.

10

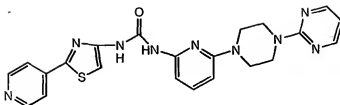
Example 144

15

**Ethyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridine-2-thiocarboxamide**

EI-MS m/z 385.5 (M+H). Calc'd for  $C_{17}H_{16}N_6OS_2$ : 384.08.

- 229 -

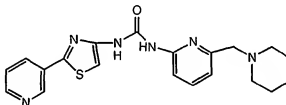
Example 145

5

1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(4-pyrimidin-2-yl-  
piperazin-1-yl)pyridin-2-yl]urea

EI-MS m/z 460.5 (M+H). Calc'd for C<sub>22</sub>H<sub>21</sub>N<sub>9</sub>OS: 459.16.

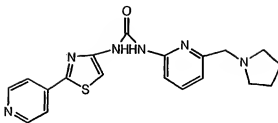
10

Example 146

15 1-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-3-  
yl-thiazol-4-yl)-urea

EI-MS m/z 395.5 (M+H). Calc'd for C<sub>20</sub>H<sub>22</sub>N<sub>6</sub>OS: 394.16.

- 230 -

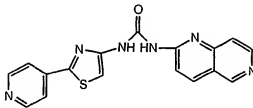
Example 147

5

1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-pyrrolidin-1-ylmethyl-pyridin-2-yl)-urea

EI-MS m/z 381.5 (M+H). Calc'd for C<sub>19</sub>H<sub>20</sub>N<sub>6</sub>OS: 380.14.

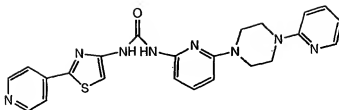
10

Example 148

15 1-[1,6]Naphthyridin-2-yl-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 349.5 (M+H). Calc'd for C<sub>17</sub>H<sub>12</sub>N<sub>6</sub>OS: 348.08.

- 231 -

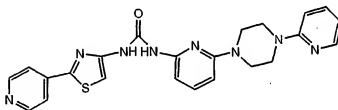
Example 149

5

1-[6-(4-Pyridin-2-yl-piperazin-1-yl)pyridin-2-yl]-3-(2-  
pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 459.5 (M+H). Calc'd for  $C_{23}H_{22}N_8OS$ : 458.16.

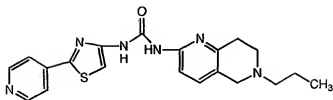
10

Example 150

15 1-[6-(4-Pyridin-2-yl-piperazin-1-yl)-pyridin-2-yl]-3-  
(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 459.5 (M+H). Calc'd for  $C_{23}H_{22}N_8OS$ : 458.16.

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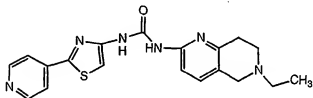
Example 151

5

1-(6-Propyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-  
3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 395.6 (M+H). Calc'd for C<sub>20</sub>H<sub>22</sub>N<sub>6</sub>OS: 394.16.

10

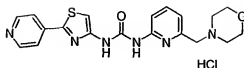
Example 152

15

1-(6-Ethyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-  
3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 381.5 (M+H). Calc'd for C<sub>19</sub>H<sub>20</sub>N<sub>6</sub>OS: 380.14.

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Example 153

5

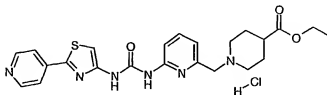
**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-morpholinylmethyl)pyridinyl]urea hydrochloride**

To a solution of N-[2-(pyridin-4-yl)-4-thiazolyl]-  
10 N'-2-(6-morpholinylmethylpyridinyl)urea (90 mg, 0.23 mmol, Example 60) in MeOH (3 mL) was added HCl (0.25 mL, 0.25 mmol, 1.0 M in Et<sub>2</sub>O). The resulting mixture was stirred at RT for 2 h then concentrated in vacuo to give a pale yellow solid.

15

The following Examples 154-165 were prepared from the corresponding amines in a manner similar to that described above for Example 153:

20

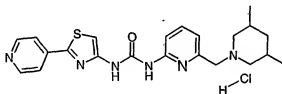
Example 154

25

**Ethyl 1-[6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl]-piperidine-4-carboxylate hydrochloride**

- 234 -

Ethyl 1-[6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl]-piperidine-4-carboxylate (50 mg, 0.05 mmol, Example 61) in MeOH (5 mL) was  
5 treated with HCl (0.12 mL, 0.06 mmol, 1M in Et<sub>2</sub>O) to afford the title salt as a yellow solid.

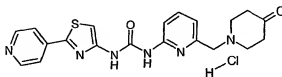
Example 155

10

1-[6-(3,5-Dimethylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-ylthiazol-4-yl)urea hydrochloride

15 1-[6-(3,5-Dimethylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-ylthiazol-4-yl)urea (52 mg, 0.123 mmol, Example 64) was treated with HCl (0.08 mL, 0.135 mmol, 1 M in Et<sub>2</sub>O) to afford the title salt as a yellow solid.

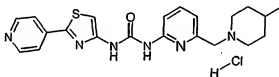
20

Example 156

25 1-[6-(4-Oxo-piperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride

- 235 -

1-[6-(4-Oxo-piperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea (30 mg, 0.073 mmol, Example 175) was treated with HCl (0.08 mL, 0.081 mmol, 5 1M in Et<sub>2</sub>O) to afford the title salt as a yellow solid.

Example 157

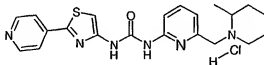
10

1-[6-(4-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride

1-[6-(4-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea (70 mg, 0.171 mmol, 15 Example 65) was treated with HCl (0.19 mL., 0.188 mmol, 1M in Et<sub>2</sub>O) to afford the title salt as a yellow solid.

Example 158

20



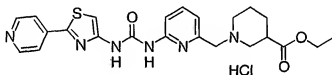
1-[6-(2-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride

25

- 236 -

1-[6-(2-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-  
3-(2-pyridin-4-yl-thiazol-4-yl)urea (70 mg, 0.171 mmol,  
Example 66) was treated with HCl (0.19 mL, 0.188 mmol,  
1M in Et<sub>2</sub>O) to afford the title salt as a yellow solid.

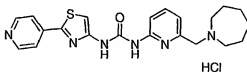
5

**Example 159**

10      **Ethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-  
pyridin-2-ylmethyl}piperidine-3-carboxylate  
hydrochloride**

HCl (0.21 mL, 0.212 mmol, 1.0 M soln in Et<sub>2</sub>O) was  
15 added to ethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-  
yl)ureido]-pyridin-2-ylmethyl}piperidine-3-carboxylate  
(90 mg, 0.193 mmol, Example 73) in a solution of MeOH  
(2 mL) to give a pale yellow solid.

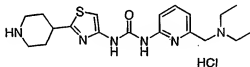
20

**Example 160**

25      **1-(6-Azepan-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-  
thiazol-4-yl)urea hydrochloride**

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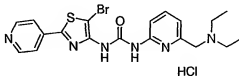
HCl (0.29 mL, 0.28 mmol, 1.0 M soln in Et<sub>2</sub>O) was added to 1-(6-azepan-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea (106 mg, 0.26 mmol, Example 71) in a solution of MeOH (4 mL) and the  
5 resulting mixture stirred 6 h. Concentration in vacuo gave a yellow solid.

**Example 161**

10

**1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-piperidin-4-yl-thiazol-4-yl)urea hydrochloride**

15 HCl (27  $\mu$ L, 0.026 mmol, 1.0 M soln in Et<sub>2</sub>O) was added to 1-(6-diethylaminomethyl-pyridin-2-yl)-3-(2-piperidin-4-yl-thiazol-4-yl)urea (11 mg, 0.026 mmol, Example 179) in a solution of MeOH (1 mL) and the  
20 resulting mixture stirred 3 h. Concentration in vacuo gave a yellow solid.

**Example 162**

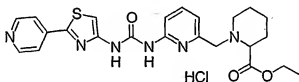
25

**1-[5-Bromo-2-(pyridin-4-yl)thiazol-4-yl]-3-(6-diethylaminomethyl-pyridin-2-yl)urea hydrochloride**

- 238 -

HCl (54  $\mu$ L, 0.054 mmol, 1.0 M soln in Et<sub>2</sub>O) was added to 1-[5-bromo-2-(pyridin-4-yl)thiazol-4-yl]-3-(6-diethylaminomethyl-pyridin-2-yl)urea (25 mg, 0.054 mmol, Example 180) in a solution of MeOH (0.5 mL) to give a yellow solid.

Example 163

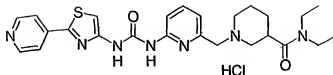


**Ethyl 1-[6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl]-piperidine-2-carboxylate hydrochloride**

15

HCl (0.12 mL, 0.12 mmol, 1.0 M soln in Et<sub>2</sub>O) was added to ethyl 1-[6-[3-(2-(pyridin-4-yl)thiazol-4-yl)ureido]pyridin-2-ylmethyl]piperidine-2-carboxylate (50 mg, 0.11 mmol, Example 74) in a solution of MeOH (2 mL) to give a pale yellow solid.

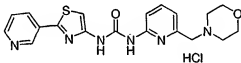
- 239 -

Example 164

5        **N,N-Diethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-  
ureido]pyridin-2-ylmethyl}piperidine-3-carboxamide  
hydrochloride**

HCl (0.15 mL, 0.156 mmol, 1.0 M soln in Et<sub>2</sub>O) was  
10 added to N,N-diethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-  
yl)-ureido]pyridin-2-ylmethyl}piperidine-3-carboxamide  
(70 mg, 0.142 mmol, Example 75) in a solution of MeOH  
(3 mL) to give a pale yellow solid.

15        **Example 165**



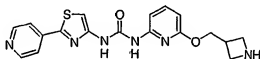
20        **1-[6-(Morpholin-4-ylmethyl)-pyridin-2-yl]-3-[(2-  
pyridin-3-yl)thiazol-4-yl]urea hydrochloride**

HCl (55  $\mu$ L, 0.05 mmol, 1.0 M in Et<sub>2</sub>O) was added to  
1-[6-(morpholin-4-ylmethyl)-pyridin-2-yl]-3-[(2-  
pyridin-3-yl)thiazol-4-yl]urea (20 mg, 0.05 mmol,  
25 Example 180) in a solution of MeOH (1 mL) and the  
resulting mixture stirred 3 h. Concentration in vacuo  
gave a yellow solid.

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The following Examples 166-167 were prepared from the corresponding protected amines in a manner similar to that described above for Example 157:

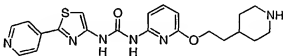
5

Example 166

10 1-[6-(Azetidin-3-ylmethoxy)pyridin-2-yl]-3-[2-(pyridin-4-yl)thiazol-4-yl]urea

From tert butyl 3-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxymethyl}-azetidine-1-

15 carboxylate (Example 80) EI-MS  $m/z$  382.2 (M+H). Calc'd for  $C_{18}H_{18}N_6O_2S$ : 382.12.

Example 167

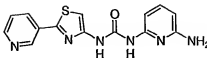
20

1-[6-(2-Piperidin-4-yl-ethoxy)pyridin-2-yl]-3-[2-(pyridin-4-yl)thiazol-4-yl]urea

25

From tert butyl 4-(2-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridin-2-yloxy}ethyl)piperidine-1-carboxylate (Example 81) MS  $m/z$ : 425 (M+1)<sup>+</sup>. Calc'd for  $C_{21}H_{24}N_6O_2S$ : 424.17.

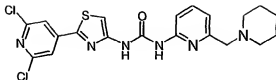
- 241 -

Example 168

5    **N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-[6-aminopyridin-2-yl]urea**

- TEA (0.27 mL, 1.94 mmol) was added to a solution of 2-(pyridin-3-yl)thiazole-4-carboxylic acid (200 mg, 0.97 mmol) and 4A molecular sieves in THF (25 mL) under N<sub>2</sub> at RT. (PhO)<sub>2</sub>PON<sub>3</sub> (0.33 mL, 1.55 mmol) followed by 2,6-diaminopyridine (265 mg, 2.43 mmol) was added and the resulting mixture was heated at reflux for 12 h. After cooling to RT, the heterogeneous mixture was
- 15    decanted to remove the molecular sieves. The precipitate was collected, rinsing with EtOAc to give a light tan solid. MS m/z: 313.0 (M+H). Calc'd for C<sub>14</sub>H<sub>12</sub>N<sub>6</sub>OS: 312.08.
- 20    The following compounds were prepared from the corresponding amines in a manner similar to that described above for Example 168:

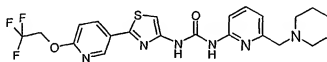
- 242 -

Example 169

5

1-[2-(2,6-Dichloropyridin-4-yl)thiazol-4-yl]-3-[6-(piperidin-1-ylmethyl)pyridin-2-yl]urea

2-(2,6-Dichloropyridin-4-yl)thiazol-4-carboxylic acid (100 mg, 0.36 mmol), 2-amino-6-piperidinylmethyl-pyridine (76 mg, 0.39 mmol), (PhO)<sub>2</sub>PON<sub>3</sub> (0.1 mL, 0.55 mmol), and TEA (0.08 mL, 0.55 mmol) were heated in toluene (15 mL) to yield the title compound as white solid. MS m/z: 464.3 (M+H). Calc'd. for C<sub>20</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>6</sub>OS -  
15 463.39.

Example 170

20

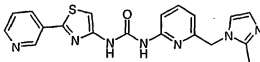
1-[6-(2,2,2-trifluoroethoxy)pyridin-3-yl]thiazol-4-yl]-3-[2-[6-(piperidin-1-ylmethyl)pyridin-2-yl]urea

2-(4-Trifluoroethoxypyridin-4-yl)thiazol-4-carboxylic acid (150 mg, 0.49 mmol), 2-amino-6-piperidinylmethyl-pyridine (104 mg, 0.54 mmol),  
25

- 243 -

(PhO)<sub>2</sub>PON<sub>3</sub> (0.16 mL, 0.74 mmol), and TEA (0.1 mL, 0.74 mmol) were heated in toluene (15 mL) to yield the title compound as white solid. MS *m/z*: 493.6 (M+H). Calc'd. for C<sub>22</sub>H<sub>23</sub>F<sub>3</sub>N<sub>6</sub>O<sub>2</sub>S - 492.52.

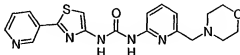
5

Example 171

10     1-[6-(2-Methylimidazol-1-ylmethyl)pyridin-2-yl]-3-[2-  
(pyridin-3-yl)thiazol-4-yl]urea

2-(Pyridin-3-yl)-4-thiazole-4-carboxylic acid (75 mg, 0.36 mmol), 2-amino-6-[2-methylimidazol-1-yl]methyl-pyridine (75 mg, 0.40 mmol), (PhO)<sub>2</sub>PON<sub>3</sub> (0.12 mL, 0.54 mmol), and TEA (0.1 mL, 0.54 mmol) were heated in toluene (15 mL) to yield the title compound as light brown solid. MS *m/z*: 392.3 (M+H). Calc'd. for C<sub>19</sub>H<sub>17</sub>N<sub>7</sub>OS - 391.45.

20

Example 172

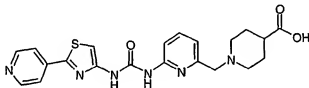
25     1-[6-(Morpholin-4-ylmethyl)-pyridin-2-yl]-3-[2-  
pyridin-3-yl)thiazol-4-yl]urea

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TEA (0.27 mL, 1.94 mmol) was added to a solution of 2-(pyridin-3-yl)thiazole-4-carboxylic acid (200 mg, 0.97 mmol) and 4A molecular sieves in THF (25 mL) under N<sub>2</sub> at RT. (PhO)<sub>2</sub>PON<sub>3</sub> (0.33 mL, 1.55 mmol) followed by  
5 2-amino, 6-morpholinylmethylpyridine (280 mg, 1.45 mmol) was added and the resulting mixture was heated at reflux for 12 h. After cooling to RT, the heterogeneous mixture was decanted to remove the molecular sieves. The precipitate was collected,  
10 rinsed with EtOAc and purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5) to give a white solid.  
MS m/z: 397.1 (M+H). Calc'd for C<sub>19</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>S - 396.47.

Example 173

15



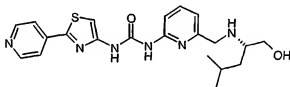
1-{6-[3-(2-(4-pyridinyl)-4-thiazolyl)ureido]-pyridin-2-ylmethyl}-piperidine-4-carboxylic acid

20

Ethyl 1-{6-[3-(2-(pyridin-4-yl)thiazol-4-yl)ureido]-pyridin-2-ylmethyl}-piperidine-4-carboxylate (55 mg, 0.12 mmol, Example 61) was suspended in MeOH (10 ml) followed by adding LiOH (50 mg, 1.18 mmol) in  
25 H<sub>2</sub>O (1 ml). The resulting mixture was heated at 45°C for 15 h. After cooling to RT, the solvent was removed. The residue was suspended in H<sub>2</sub>O (20 mL). The pH was adjusted to 7 using HCl (1N). The resulting

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mixture was extracted with  $\text{CHCl}_3$ : $\text{IPOH}$  (3:1). The organic layer was washed with  $\text{H}_2\text{O}$  and brine. After being dried over anhydrous  $\text{MgSO}_4$ , the solvent was removed in *vacuo* to yield the final compound as light yellow solid. MS  $m/z$ : 438.7 (M+H). Calc'd. for  $\text{C}_{21}\text{H}_{22}\text{N}_6\text{O}_3\text{S}$  - 438.51.

**Example 174**

10

**1-{6-[(1-Hydroxymethyl-3-methylbutylamino)methyl]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

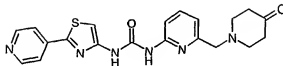
tert-Butyl (1-hydroxymethyl-3-methyl-butyl)-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl)-carbamate (165 mg, 0.313 mmol, Example 62) in  $\text{MeOH}$  (5 mL) was treated with  $\text{HCl}$  (0.16 mL, 0.627 mmol, 4M in dioxane). The resulting stirred solution was heated at  $40^\circ\text{C}$  in closed system for 15 h. After cooling to RT, the pH was adjusted to 7 using 1 N  $\text{NaOH}$ . Solvent was removed and the residue was extracted with  $\text{CHCl}_3$ . The organic layer was washed with  $\text{H}_2\text{O}$ , brine, dried over  $\text{MgSO}_4$ , and concentrated to yield a brown liquid crude product. This crude product was purified by chromatography on silica gel. Elution with  $\text{CH}_2\text{Cl}_2$ : $\text{MeOH}$  mixture (95:5) gave final compound as a tan

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solid. MS  $m/z$ : 427.2 (M+H). Calc'd. for  $C_{21}H_{26}N_6O_2S$  - 426.54.

**Example 175**

5



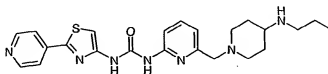
**1-[6-(4-Oxo-piperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

10

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(4-ethoxyacetal)piperidylmethyl]urea (300 mg, 0.66 mmol) in THF (15 mL) was treated with 5N HCl (5 mL). The resulting mixture was heated to reflux under  $N_2$  for 5 h. After cooling to RT, the mixture was basified using 5 N NaOH. Solvent was removed and the residue was extracted with  $CHCl_3$ . The organic layer was washed with  $H_2O$ , brine, dried over  $MgSO_4$ , and concentrated to yield a pale yellow solid. MS  $m/z$ : 409.3 (M+H).  
20 Calc'd. for  $C_{20}H_{20}N_6O_2S$  - 408.32.

**Example 176**

25

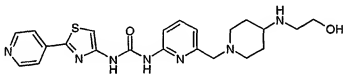


**1-[6-[4-(Propylamino)piperidin-1-ylmethyl]pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

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To a suspension of N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(piperidon-4-yl)methyl]urea (50 mg, 0.12 mmol, Example 175) in MeOH (10 mL) was added  
5 propylamine (0.1 mL, 1.22 mmol). The resulting mixture was heated at 50°C for 4 h under N<sub>2</sub>. After the mixture was cooled to RT, NaBH<sub>4</sub> (83 mg, 2.20 mmol) was added. The mixture was stirred at RT under N<sub>2</sub> for 3 h. Solvent was removed in vacuo and the crude product was  
10 purified by chromatography on silica gel. Elution with CH<sub>2</sub>Cl<sub>2</sub>:MeOH (90:10) gave the title compound as a white solid. MS m/z: 451.7 (M+H). Calc'd. for C<sub>23</sub>H<sub>29</sub>N<sub>7</sub>OS - 451.6:

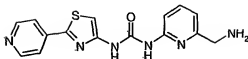
15

Example 177

1-(6-[4-(2-Hydroxyethylamino)piperidin-1-ylmethyl]-  
20 pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(piperidon-4-yl)methyl]urea (60 mg, 0.147 mmol, Example 175) and ethanolamine (0.09 mL, 1.47 mmol) were heated  
25 in MeOH (10 mL) yielded the title compound as pale yellow solid. MS m/z: 454.6 (M+H). Calc'd. for C<sub>22</sub>H<sub>27</sub>N<sub>7</sub>O<sub>2</sub>S - 453.57.

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Example 178

5

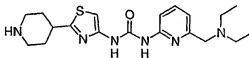
**N-(6-Aminomethyl-2-pyridyl)-N'-[2-(4-pyridinyl)-4-thiazolyl]urea**

Pd(OH)<sub>2</sub> (70 mg, 0.5 mmol) was suspended in EtOH (5 mL) followed by adding N-(6-azidomethyl-2-pyridyl)-N'-[2-(4-pyridinyl)-4-thiazolyl]urea (70 mg, 0.198 mmol, Example 69) in EtOH (8 mL). The resulting mixture was heated at 45°C under H<sub>2</sub> balloon for 3 h. After cooling to RT, the mixture was filtered by passing through 2 layers of pleated filtered papers. Solvent was removed in vacuo to yield the final compound as a yellow solid. MS m/z: 327.3 (M+H). Calc'd. for C<sub>15</sub>H<sub>14</sub>N<sub>6</sub>OS - 326.38.

15

Example 179

20



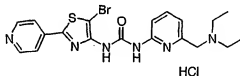
**1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-piperidin-4-yl-thiazol-4-yl)urea**

25

Lithium triethylborohydride (0.84 mL, 0.84 mmol, 1.0 M in THF) was added to a solution of 1-(6-diethylamino-methyl-pyridin-2-yl)-3-(2-pyridin-4-yl-

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thiazol-4-yl)urea (100 mg, 0.24 mmol, Example 117) and DIEA (63  $\mu$ L, 0.36 mmol) in THF (5 mL) and the resulting mixture was stirred 6 h at RT. The reaction was quenched via dropwise addition of MeOH and concentrated in vacuo. Purification by preparative HPLC (5-60%  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ ) gave a white solid. MS  $m/z$ : 389.2 (M+H). Calc'd for  $\text{C}_{19}\text{H}_{28}\text{N}_6\text{OS}$  - 388.53.

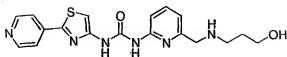
**Example 180**

**1-[5-Bromo-2-(pyridin-4-yl)thiazol-4-yl]-3-(6-diethylaminomethylpyridin-2-yl)urea**

15

Bromine (46  $\mu$ L, 0.90 mmol) was added to a solution of 1-(6-diethylaminomethylpyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea (190 mg, 0.45 mmol, Example 117) in MeOH (8 mL) and the resulting solution was stirred at RT for 1 h. The reaction was quenched with saturated sodium bisulfite solution and concentrated in vacuo. The residue was dissolved in  $\text{CHCl}_3/\text{IPOH}$  (3/1, 10 mL) and washed with  $\text{H}_2\text{O}$  (3x10 mL) followed by 1N NaOH solution (10 mL). The organics were combined, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo to give a yellow solid. MS  $m/z$ : 461.1 (M+H). Calc'd for  $\text{C}_{19}\text{H}_{21}\text{BrN}_6\text{OS}$  - 461.39.

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Example 181

5    1-(6-[(3-Hydroxypropylamino)methyl]-pyridin-2-yl)-3-(2-  
pyridin-4-yl-thiazol-4-yl)urea

## Step A

- 2-(4-Pyridinyl)-4-thiazolcarbonylazide (220 mg,  
10    0.78 mmol) and 2-amino-6-[(N''-tert-butoxycarbonyl-N''-3-hydroxypropyl)amino]methylpyridine (196 mg, 0.94 mmol) in dry toluene (10 mL) were heated at 100°C for 12 h to give a pale yellow solid which was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5) to  
15    give N-[2-(pyridin-4-yl)-4-thiazolyl]-N'-2-[6-(N''-tert-butoxycarbonyl-N''-(3-hydroxypropyl)-amino)methylpyridinyl] urea as a white solid. MS m/z: 485.2 (M+H). Calc'd for C<sub>23</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub>S - 484.58.

## 20    Step B

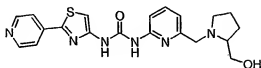
- HCl (112 µL, 0.112 mmol, 1.0 M in Et<sub>2</sub>O) was added to a solution of N-[2-(pyridin-4-yl)-4-thiazolyl]-N'-2-[6-(N''-tert-butoxycarbonyl-N''-(3-hydroxypropyl)-amino)methylpyridinyl] urea (25 mg, 0.051 mmol, Step A)  
25    in MeOH (1 mL) and the resulting mixture was heated at 45°C for 12 h. A yellow precipitate formed and was filtered off, rinsing with hexane. The precipitate was added to CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and washed with 1N NaOH solution (5 mL). The organics were collected, dried  
30    over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give a pale

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yellow solid. MS  $m/z$ : 385.0 (M+H). Calc'd for  $C_{18}H_{20}N_6O_2S$  - 384.62.

Example 182

5



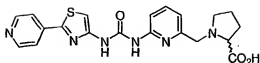
**1-[6-(2-Hydroxymethylpyrrolidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

10

$LiAlH_4$  (3 mg, 0.079 mmol) was added to a solution of methyl 1-[6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl]-pyrrolidine-2-carboxylate (15 mg, 0.034 mmol, Example 77) in THF (5 mL) at RT and the resulting mixture was stirred for 8 h. A precipitate formed and was collected. The solid was dissolved in  $CHCl_3$  (5 mL) and washed with saturated  $NaHCO_3$  solution (5 mL). The aqueous layer was adjusted to pH 7 with 1N HCl and extracted with  $CHCl_3$ . The organics were combined, dried over  $MgSO_4$  and concentrated in vacuo to give a pale yellow solid. MS  $m/z$ : 411.1 (M+H). Calc'd for  $C_{20}H_{22}N_6O_2S$  - 410.50.

20

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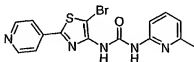
Example 183

5

**1-{6-[3-(2-Pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl}-pyrrolidine-2-carboxylic acid**

A 1.0 N NaOH solution (0.40 mL) was added to a solution of methyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl}pyrrolidine-2-carboxylate (3 mg, 6.84  $\mu$ M, Example 77) in MeOH (1 mL) and the resulting mixture stirred at RT for 12 h. The mixture was adjusted to pH 7 with 1N HCl solution and concentrated in vacuo. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and a few drops of MeOH. A precipitate formed and was collected to give a white solid. MS  $m/z$ : 423.5 (M-H) Calc'd for  $\text{C}_{20}\text{H}_{20}\text{N}_6\text{O}_3\text{S}$  - 424.48.

20

Example 184

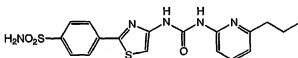
25

**1-(5-Bromo-(2-pyridin-4-yl)thiazol-4-yl)-3-(6-methylpyridin-2-yl)urea**

NBS (686 mg, 3.85 mmol) and AIBN (158 mg, 0.96 mmol) were added to a heterogeneous solution of 1-((2-

- 253 -

pyridin-4-yl)thiazol-4-yl)-3-(6-methylpyridin-2-yl)urea (600 mg, 1.93 mmol, Example 6) in  $\text{CCl}_4$  (25 mL) and the resulting mixture was heated at reflux for 2 h. After cooling to RT, a precipitate formed and was collected, 5 rinsing with hexane to give a white solid. MS  $m/z$ : 392.0 ( $M+2H$ ). Calc'd for  $\text{C}_{15}\text{H}_{12}\text{BrN}_5\text{OS}$  - 390.26.

**Example 185**

10

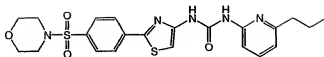
**4-{4-[3-(6-Propyl-pyridin-2-yl)-ureido]-thiazol-2-yl}-benzenesulfonamide**

15 In an oven-dried, 50-mL, round-bottomed flask were placed 2-(p-sulfamoylphenyl)thiazole-4-carboxylic acid (250 mg, 0.82 mmol), molecular sieves (800 mg) in THF (20 mL). To this mixture was added  $\text{Et}_3\text{N}$  (0.23 mL, 1.64 mmol), followed by DPPA (0.28 mL, 1.28 mmol). The 20 reaction was stirred for 5 min, then 6-propylpyridine-2-amine (280 mg, 2.06 mmol) was added. The suspension was heated to  $75^\circ\text{C}$  for 14 h, cooled to RT, diluted with  $\text{H}_2\text{O}$  (10 mL) and  $\text{EtOAc}$  (150 mL), and filtered to remove molecular sieves. The filtrate was concentrated in 25 vacuo to give the crude product as a yellow solid which was filtered, washed with  $\text{H}_2\text{O}$  (3 x 10 mL),  $\text{EtOAc}$  (1 x 10 mL) and  $\text{Et}_2\text{O}$  (3 x 10 mL) to afford the title compound as a yellow solid. MS  $m/z$ : 418 ( $M+H$ ). Calc'd for  $\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_3\text{S}_2$ : 417.09.

30

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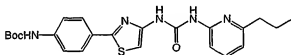
### Example 186



5 1-{2-[4-(4-Morpholinylsulfonyl)phenyl]thiazol-4-yl}-3-  
(6-propylpyridin-2-yl)urea

In a manner similar to that described for the preparation of Example 185, 2-((4-morpholinylsulfonyl)-10-phenyl)thiazole-4-carboxylic acid (354 mg) was treated with DPPA and 6-propylpyridine-2-amine to give the title compound. MS m/z: 488 (M+H). Calc'd for C<sub>22</sub>H<sub>26</sub>N<sub>6</sub>O<sub>4</sub>S<sub>2</sub>: 487.13.

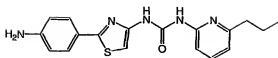
15 Example 187



tert-Butyl (4-{4-[3-(6-propylpyridin-2-yl)ureido]-  
thiazol-2-yl}phenyl)carbamate

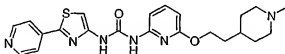
In a manner similar to that described for the preparation of Example 185, 2-[4-(N-Boc-amino)-phenyl]-thiazole-4-carboxylic acid (130 mg) was treated with DPPA and 6-propylpyridine-2-amine to give the title compound. MS m/z: 454.5 (M+H). Calc'd for C<sub>23</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub>S: 453.18.

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Example 188

5    1-[2-(4-Aminophenyl)thiazol-4-yl]-3-(6-propylpyridin-2-yl)urea

In an oven-dried, 25-mL, round-bottomed flask were placed N-[6-propylpyridine]-N'-[4-[N-Bocaminophenyl]-4-thiazolyl]urea (55 mg, 0.12 mmol, Example 187),  
 10    thioanisole (0.35 mL) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). TFA (0.35 mL) was added, the mixture was stirred at RT for 6 h then concentrated in vacuo. Purification by flash chromatography on silica gel [EtOAc/hexane (extracted  
 15    with aq. NH<sub>4</sub>OH), 40:60] afforded the title compound.  
 MS m/z: 354.0 (M+H). Calc'd for C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>OS: 353.13.

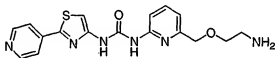
Example 189

20    1-[6-[2-(1-Methylpiperidin-4-yl)ethoxy]pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

25    A mixture of N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(4-piperidinylethoxy)pyridinyl]urea (0.17 g, 0.40 mmol, Example 167), paraformaldehyde (0.17 g), and NaBH(OAc)<sub>3</sub> (0.21 g, 1.0 mmol) in 40 mL of CH<sub>2</sub>Cl<sub>2</sub> was

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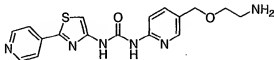
stirred at RT under N<sub>2</sub> for 12 h. After 12 h, the solvent was removed in vacuo, and the residue was diluted with 20 mL of H<sub>2</sub>O, then extracted with CHCl<sub>3</sub>/IpOH (3:1, 3X20 mL). The combined organic portions were washed with brine, and dried over MgSO<sub>4</sub>, and the solvents were removed in vacuo to yield a residue. Purification over silica gel (gradient, 5 % to 7.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> with 0.5% of TEA) provided the title compound as an off-white solid. MS m/z: 439 (M+H). Calc'd for C<sub>22</sub>H<sub>26</sub>N<sub>6</sub>O<sub>2</sub>S: 438.18.

Example 190

15

1-[6-(2-Aminoethoxymethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

Prepared in a manner similar to that described in Example 189. MS m/z: 371 (M+H). Calc'd for C<sub>17</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub>S: 370.12.

Example 191

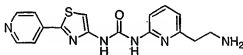
25

1-[5-(2-Aminoethoxymethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

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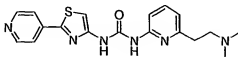
Prepared in a manner similar to that described in Example 189. MS  $m/z$ : 371 (M+H). Calc'd for  $C_{17}H_{18}N_6O_2S$ : 370.12.

5

Example 192

10     1-{6-[2-Aminoethyl]pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea

To a mixture of 1-{6-[2-(phthalimidyl)ethyl]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea (75  
15 mg, 0.16 mmol, Example 88) and EtOH (10 mL) was added hydrazine hydrate (0.1 mL, 0.18 mmol). The mixture was heated at reflux for 2 h then was cooled to RT. The residue was dissolved in 3:1  $CHCl_3$ /IPOH, washed with saturated  $NaHCO_3$ ; dried ( $MgSO_4$ ) and concentrated in  
20 vacuo to afford the title compound as a yellow solid. MS  $m/z$ : 341.0 (M+H). Calc'd for  $C_{16}H_{16}N_6OS$ : 340.11.

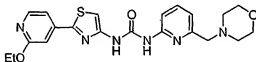
Example 193

25

1-{6-[2-(N,N-Dimethylamino)ethyl]pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea

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To a solution of 1-{6-[2-aminoethyl]pyridin-2-yl}-  
3-(2-pyridin-4-yl-thiazol-4-yl)urea (20 mg, 0.06 mmol,  
Example 192) and  $\text{CH}_2\text{Cl}_2$  (5 mL) was added  
5 paraformaldehyde (20 mg) and  $\text{NaBH}(\text{OAc})_3$  (30 mg, 0.14  
mmol). The mixture was stirred at RT for 2.5 h.  
Extracted with 3:1  $\text{CHCl}_3/\text{IPOH}$  and washed with brine;  
dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to afford the  
desired compound as a yellow solid. MS m/z: 369.1  
10 (M+H). Calc'd for  $\text{C}_{18}\text{H}_{20}\text{N}_6\text{OS}$ : 368.14.

**Example 194**

15

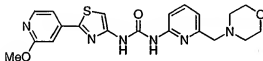
**1-[2-(2-Ethoxypyridin-4-yl)thiazol-4-yl]-3-(6-  
morpholin-4-ylmethyl-pyridin-2-yl)urea**

To a mixture of 1-[2-(2-chloropyridin-4-  
20 yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-  
yl)urea (100 mg, 0.23 mmol, Example 90) and EtOH (50  
mL) was added a 21 wt% NaOEt/EtOH solution (0.4 mL, 1.2  
mmol) and DMF (2 mL). The mixture was heated to reflux  
for 15 h then additional 21 wt% NaOEt/EtOH solution (10  
25 mL) were added. After 2.5 h, the reaction was complete  
as judged by LC/MS. The reaction mixture was  
concentrated in vacuo then diluted with EtOAc and the  
solid was filtered off. The filtrate was concentrated  
in vacuo to afford an orange slushy oil which was  
30 purified by silica flash chromatography (5-10%

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MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a yellow solid. MS m/z: 441.1 (M+H). Calc'd for C<sub>21</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub>S: 440.16.

5

Example 195

10

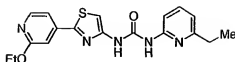
**1-[2-(2-Methoxypyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea**

To a mixture of 1-[2-(2-chloropyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea (100 mg, 0.23 mmol, Example 90) and MeOH (50 mL) was added solid NaOMe (1.6 g, 29.6 mmol) and DMF (20 mL). The reaction mixture was heated to 130°C. After 2 h, the reaction mixture was cooled to RT and filtered. The filtrate was concentrated in vacuo and diluted with EtOAc and filtered to remove the solid.

The filtrate was concentrated in vacuo to afford an orange oil which was purified by silica flash chromatography (5% MeOH/ CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a white solid. MS m/z: 427.2 (M+H). Calc'd for C<sub>20</sub>H<sub>22</sub>N<sub>6</sub>O<sub>3</sub>S: 426.15.

25

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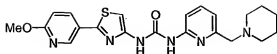
Example 196

5

1-[2-(2-Ethoxypyridin-4-yl)thiazol-4-yl]-3-(6-ethyl-  
pyridin-2-yl)urea

To a 10 mL round bottom flask containing 1-[2-(2-  
10 chloropyridin-4-yl)thiazol-4-yl]-3-(6-ethylpyridin-2-  
yl)urea (40 mg, 0.11 mmol) (prepared similar to that  
described for Example 95) was charged a 21 wt%  
NaOEt/EtOH solution (5 mL). The reaction mixture was  
heated to reflux. After 2 h, the reaction mixture was  
15 cooled to RT and diluted with H<sub>2</sub>O then concentrated in  
vacuo. The solid residue was washed with CH<sub>2</sub>Cl<sub>2</sub> and  
EtOAc then the solid was diluted with MeOH and  
concentrated in vacuo. The residue was diluted with  
EtOAc; washed with saturated NH<sub>4</sub>Cl and H<sub>2</sub>O; dried  
20 (MgSO<sub>4</sub>) and concentrated in vacuo to afford the title  
compound as a light-orange solid. MS m/z: 370.2  
(M+H). Calc'd for C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub>S: 369.13.

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Example 197

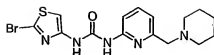
5

**1-[2-(6-Methoxypyridin-3-yl)thiazol-4-yl]-3-(6-methylpiperidin-1-ylmethylpyridin-2-yl)urea**

To a solution of the 3-(4-methoxy-3-pyridyl)thiazole carboxylic acid (200 mg, 0.85 mmol) and dry toluene (20 mL) was added (PhO)<sub>2</sub>PON<sub>3</sub> (0.2 mL, 0.94 mmol) and TEA (0.13 mL, 0.94 mmol). The mixture was heated to 85°C for five min then 2-amino-6-methylpiperdinylnpyridine (0.16 g, 0.85 mmol) in CH<sub>3</sub>CN (3 mL) was added. The reaction was heated at reflux for 15 h then concentrated in vacuo and purified by silica flash chromatography (1% to 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound as an orange oil. Diluted with MeOH (5 mL) and added one equivalent of 1M HCl in Et<sub>2</sub>O. Concentrated in vacuo to afford the HCl salt as an orange solid. MS m/z: 424.9 (M+H). Calc'd for C<sub>21</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub>S: 424.17.

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## Example 198

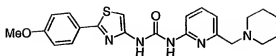


5

**1-(2-Bromothiazol-4-yl)-3-(6-(piperidin-1-ylmethyl)  
pyridin-2-yl)urea**

To a stirred suspension of 2-bromothiazole-4-  
10 carboxylic acid (5.13 g, 2 mmol) in anhydrous  $\text{CH}_3\text{CN}$  (40 ml) at RT, under  $\text{N}_2$ , TEA (3.80 ml, 27 mmol) and  $(\text{PhO})_2\text{PON}_3$  (5.90 ml, 27 mmol) were added. The resulting solution was heated to  $85^\circ\text{C}$ . Upon reaching  $85^\circ\text{C}$ , a solution of 6-(piperidylmethyl)-2-pyridylamine  
15 (4.74 g, 25 mmol) in anhydrous  $\text{CH}_3\text{CN}$  (60 ml) was added. The reaction was maintained at this temperature for 2.25 h. After cooling to RT the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (50 ml) then washed with a saturated solution of  $\text{NH}_4\text{Cl}$  (aq) (40 ml). The organic layer was  
20 separated, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (3:1/2:1/1:1, EtOAc:acetone) to yield the title compound as a pale yellow solid. MS m/z: 396 (M+H), 398 (M+3). Calc'd  
25 for  $\text{C}_{15}\text{H}_{18}\text{BrN}_5\text{OS}$ : 395.04.

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Example 199

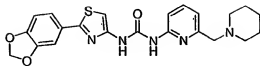
5

**1-[2-(4-Methoxyphenyl)thiazol-4-yl]-3-(6-(piperidin-1-ylmethylpyridin-2-yl)urea**

A stirred suspension of N-(2-bromo(1,3-thiazol-4-yl))([6-(piperidylmethyl)(2-pyridyl)]amino)carboxamide (2.23 g, 5.64 mmol), 4-methoxyphenylboronic acid (0.94 g, 6.21 mmol), PdCl<sub>2</sub>(dppf)<sub>2</sub> (0.46 g, 0.56 mmol) and Na<sub>2</sub>CO<sub>3</sub> (2.10 g, 17.0 mmol) in ethylene glycol dimethyl Et<sub>2</sub>O (25 ml) and H<sub>2</sub>O (8 ml) was heated at reflux for 12h. After cooling to RT the mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (3:1, EtOAc:acetone) to yield the title compound as a pale yellow amorphous solid. MS m/z: 424 (M+H). Calc'd for C<sub>22</sub>H<sub>25</sub>N<sub>5</sub>O<sub>2</sub>S: 423.17.

The following compounds were prepared from the corresponding boronic acids in a manner similar to Example 199:

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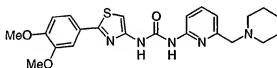
Example 200

5

1-(2-(Benzo[1,3]dioxol-5-yl)thiazol-4-yl)-3-(6-  
piperidin-1-ylmethyl-pyridin-2-yl)-urea

MS m/z: 438 (M+H). Calc'd for  $C_{22}H_{23}N_5O_3S$ : 437.15.

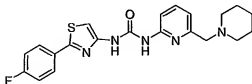
10

Example 201

15 1-[2-(3,4-Dimethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-  
1-ylmethyl-pyridin-2-yl)urea

MS m/z: 454 (M+H). Calc'd for  $C_{23}H_{27}N_5O_3S$ : 453.18.

20

Example 202

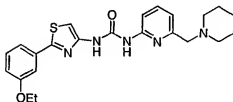
25

1-[2-(4-Fluorophenyl)thiazol-4-yl]-3-(6-piperidin-1-  
ylmethyl-pyridin-2-yl)urea

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EI-MS m/z 412 (M+H). Calc'd for  $C_{21}H_{22}FN_5OS$ : 411.15.Example 203

5

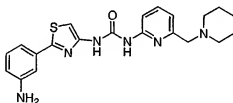


1-[2-(3-Ethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethylpyridin-2-yl)urea

10

EI-MS m/z 438 (M+H). Calc'd for  $C_{23}H_{27}N_5O_2S$ : 437.19.Example 204

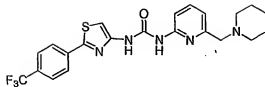
15



1-[2-(3-Aminophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethylpyridin-2-yl)urea

20 EI-MS m/z 409 (M+H). Calc'd for  $C_{21}H_{24}N_6OS$ : 408.17.

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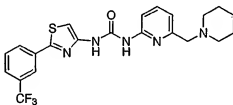
Example 205

5

1-[2-(4-Trifluoromethylphenyl)thiazol-4-yl]-3-(6-  
piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 462 (M+H). Calc'd for  $C_{22}H_{22}F_3N_5OS$ : 461.15.

10

Example 206

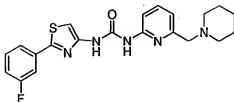
15

1-[2-(3-Trifluoromethylphenyl)thiazol-4-yl]-3-(6-  
piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 462 (M+H)<sup>+</sup>. Calc'd for Calc'd for  
 $C_{22}H_{22}F_3N_5OS$ : 461.15.

20

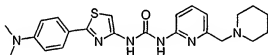
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Example 207

5

1-[2-(3-Fluorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 412 (M+H). Calc'd for C<sub>21</sub>H<sub>22</sub>FN<sub>5</sub>OS:  
10 411.15.

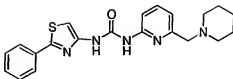
Example 208

15

1-[2-(4-Dimethylaminophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 437 (M+H). Calc'd for C<sub>23</sub>H<sub>28</sub>N<sub>6</sub>OS: 436.20.  
20

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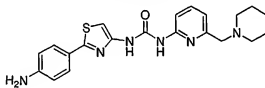
Example 209

5

1-[2-phenylthiazol-4-yl]-3-(6-piperidin-1-ylmethyl-  
pyridin-2-yl)urea

EI-MS m/z 394 (M+H). Calc'd for C<sub>21</sub>H<sub>23</sub>N<sub>5</sub>OS: 393.16.

10

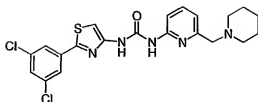
Example 210

15

1-[2-(4-Aminophenyl)thiazol-4-yl]-3-(6-piperidin-1-  
ylmethyl-pyridin-2-yl)urea

EI-MS m/z 409 (M+H). Calc'd for C<sub>21</sub>H<sub>24</sub>N<sub>6</sub>OS: 408.17.

- 269 -

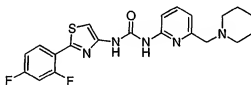
Example 211

5

1-[2-(3,5-Dichlorophenyl)thiazol-4-yl]-3-(6-piperidin-  
1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 462 (M+H). Calc'd for C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>5</sub>OS: 461.08.

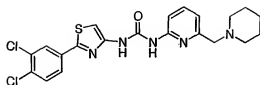
10

Example 212

15 1-[2-(2,4-Difluorophenyl)thiazol-4-yl]-3-(6-piperidin-  
1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 430 (M+H). Calc'd for C<sub>21</sub>H<sub>21</sub>F<sub>2</sub>N<sub>5</sub>OS: 429.14.

- 270 -

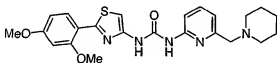
Example 213

5

1-[2-(3,4-Dichlorophenyl)thiazol-4-yl]-3-(6-piperidin-  
1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 462 (M+H). Calc'd for  $C_{21}H_{21}Cl_2N_5OS$ : 461.08.

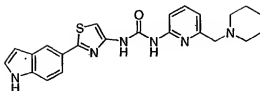
10

Example 213a

15 1-[2-(2,4-Dimethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-  
1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 454 (M+H). Calc'd for  $C_{23}H_{27}N_5O_3S$ : 453.18.

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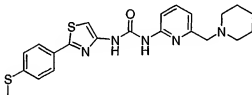
Example 214

5

1-[2-(1H-Indol-5-yl)-thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea

EI-MS m/z 433 (M+H). Calc'd for C<sub>23</sub>H<sub>24</sub>N<sub>6</sub>OS: 432.17.

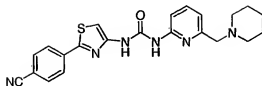
10

Example 215

15 1-[2-(4-Methylthiophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 440 (M+H). Calc'd for C<sub>22</sub>H<sub>25</sub>N<sub>5</sub>OS<sub>2</sub>: 439.15.

- 272 -

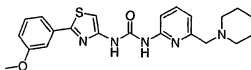
Example 216

5

1-[2-(4-Cyanophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 419 (M+H). Calc'd for C<sub>22</sub>H<sub>22</sub>N<sub>6</sub>OS: 418.16

10 Mol. Wt.: 418.5.

Example 217

15

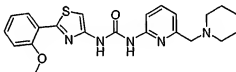
1-[2-(3-Methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

To a stirred solution of 2-(3-methoxyphenyl)-1,3-thiazole-4-carboxylic acid (0.17 g, 0.72 mmol) in  
20 toluene (10 mL) at RT and under N<sub>2</sub> was added TEA (0.2 mL). After 5 min, (PhO)<sub>2</sub>PON<sub>3</sub> (0.2 5mL) was added and the reaction mixture was heated at 85°C for 20 min followed by the addition of 6-(piperidylmethyl)-2-pyridylamine (0.21 g, 1.1 mmol). The resulting mixture  
25 was heated at reflux for 4 h using a Dean-Stark trap.

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The mixture was cooled to RT, concentrated by rotary evaporation and purified on silica gel (5:95 MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The yellow solid obtained was dissolved in EtOAc (15mL) and washed with a saturated solution of NH<sub>4</sub>Cl (aq). The organic phase was separated, dried over MgSO<sub>4</sub>, filtered and concentrated by rotary evaporation. The product was recrystallized from hexanes to afford the title compound as a white solid. EI-MS m/z 424 (M+H). Calc'd for C<sub>22</sub>H<sub>25</sub>N<sub>5</sub>O<sub>2</sub>S: 423.17.

10

**Example 218**

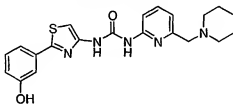
15     **1-[2-(2-Methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea**

To a stirred solution of 2-(2-methoxyphenyl)-1,3-thiazole-4-carboxylic acid (0.22 g, 0.94 mmol) in toluene (10 mL) at RT and under N<sub>2</sub> was added TEA (0.3 mL). After 5 min, (PhO)<sub>2</sub>PON<sub>3</sub> (0.32 mL) was added and the reaction mixture was heated at 85°C for 20 min followed by the addition of 6-(piperidylmethyl)-2-pyridylamine (0.27 g, 1.41 mmol). The resulting mixture was heated at reflux for 4 h using a Dean-Stark trap. The mixture was cooled to RT, concentrated by rotary evaporation and purified on silica gel (5:95 MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The yellow solid obtained was dissolved in EtOAc (15 mL) and washed with saturated NH<sub>4</sub>Cl (10

- 274 -

mL). The organic phase was separated, dried over  $\text{MgSO}_4$ , filtered and concentrated by rotary evaporation to afford the title compound as a pale-yellow solid. EI-MS  $m/z$  424 (M+H). Calc'd for  $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}_2\text{S}$ : 423.17.

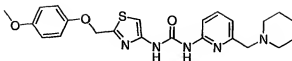
5

Example 219

10 **1-[2-(3-Hydroxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea**

A mixture of 1-[2-(3-methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea (Example 218) and beryllium chloride (5.0 eq) in dry toluene (0.2 M) and 4Å° molecular sieves was heated at reflux for 10 h. The starting material was not totally soluble in toluene. The mixture was brought to RT, diluted with EtOAc and washed with saturated  $\text{NH}_4\text{Cl}$ . The organic phase was separated, dried over  $\text{MgSO}_4$ , filtered, concentrated by rotary evaporation and purified by prep HPLC (Column Phenomenex type Prodigy 50 ODS3 100A size 250x21.20mm 5u, Gradient 10% to 90%  $\text{CH}_3\text{CN}:\text{H}_2\text{O}$  containing 1% TFA over 20 min, Detector 254 nm, 4 nm Band) to afford the title compound as an off white solid. EI-MS  $m/z$  410 (M+H). Calc'd for  $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_2\text{S}$ : 409.16.

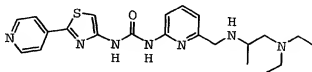
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Example 220

5

1-[2-(4-Methoxyphenoxy)methyl]thiazol-4-yl]-3-(6-  
piperidin-1-ylmethyl-pyridin-2-yl)urea

To a stirred solution of 2-[(4-methoxyphenoxy)-  
10 methyl]-1,3-thiazole-4-carboxylic acid (0.10 g, 0.38  
mmol) and TEA (0.06 mL, 0.46 mmol) in dry toluene (15mL)  
and 4Å° molecular sieves was added (PhO)<sub>2</sub>PON<sub>3</sub> (0.10 mL,  
0.46 mmol). The resulting mixture was heated at 85°C  
for 25 min followed by the addition of 6-(piperidyl-  
15 methyl)-2-pyridylamine (0.09 g, 0.46 mmol). The  
resulting mixture was heated to reflux for 15 h, cooled  
to RT, filtered, concentrated by rotary evaporation and  
purified on silica gel (5:95MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the  
title compound as a yellow oil. EI-MS m/z 454 (M+H).  
20 Calc'd for C<sub>23</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub>S: 453.18.

Example 221

25

1-{6-[2-(Diethylamino-1-methylethylamino)methyl]-  
pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea

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## Step a

To a stirred solution of N-[(6-amino(2-pyridyl)methyl)-N-[2-(diethylamino)-isopropyl](tert-butoxy)-carboxamide (30 mg, 0.09 mmol) in toluene (5 mL) was added 2-aza-2-diazo-1-(2-(4-pyridyl)(1,3-thiazol-4-yl))ethen-1-one (0.02 g, 0.09 mmol). The resulting green solution was heated to reflux in a Dean-Stark trap for 1.5 h until the starting materials were consumed. The mixture was brought to RT, concentrated by rotary evaporation and the residue obtained was partitioned between H<sub>2</sub>O (10 mL) and CHCl<sub>3</sub> (10 mL). The organic phase was separated and the aqueous phase was extracted (3x10 mL) with CHCl<sub>3</sub>. The organic layers were combined, dried over MgSO<sub>4</sub>, filtered, concentrated by rotary evaporation and purified by prep TLC (10:90 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford tert butyl (2-dimethylamino-1-methyl-ethyl)-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridin-2-yl)carbamate as a white solid. EI-MS m/z 540 (M+H). Calc'd for C<sub>27</sub>H<sub>37</sub>N<sub>7</sub>O<sub>3</sub>S: 539.27.

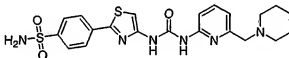
## Step B

To a stirred solution of N-[2-diethylamino)-ethyl](tert-butoxy)-N-[(6-[N-(2-(4-pyridyl)(1,3-thiazol-4-yl))carbamoyl]amino)(2-pyridyl)methyl]-carboxamide (4 mg, 0.007 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added TFA (1 mL). The resulting solution was stirred at RT and under N<sub>2</sub> atmosphere for 2 h, concentrated by rotary evaporation and the residue was diluted with EtOAc (5 mL) and washed with a saturated solution of

- 277 -

NaHCO<sub>3</sub> (aq) (15 mL). The organic phase was separated, dried over MgSO<sub>4</sub>, filtered, concentrated by rotary evaporation and purified by prep TLC (1:1 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to yield 1-{6-[(2-diethylamino-1-methylethylamino)methyl]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea. EI-MS m/z 540 (M+H). Calc'd for C<sub>22</sub>H<sub>29</sub>N<sub>7</sub>OS: 439.22.

#### Example 222



#### **4-{4-[3-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-ureido]-thiazol-2-yl}-benzenesulfonamide**

15

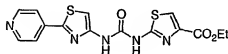
To a stirred solution of ethyl 2-(4-sulfamoyl-phenyl)-1,3-thiazole-4-carboxylic acid (90 mg, 0.32 mmol) in dry TFA (3 mL) and 4Å molecular sieves at RT and under N<sub>2</sub> was added TEA (0.1 mL). After 5 min, (PhO)<sub>2</sub>PON<sub>3</sub> (0.11 mL) and 6-(piperidylmethyl)-2-pyridylamine (0.10 g, 0.51 mmol) were added and the reaction mixture was heated to reflux for 4h and then cooled to RT. The mixture was washed with 10% HCl (aq) and extracted with EtOAc (3x10 mL). The aqueous layer was brought to a pH 8.0 and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x20mL). The extracts were combined, dried over MgSO<sub>4</sub>, concentrated by rotary evaporation and purified on silica gel (2:1 hexanes/EtOAc and 1:1 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to

- 278 -

afford the title compound as a pale yellow solid. EI-MS  $m/z$  473 (M+H). Calc'd for  $C_{21}H_{24}N_6O_3S_2$ : 472.14.

Example 223

5

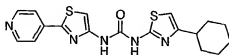


**Ethyl 2-[3-[2-(pyridin-4-yl)-thiazol-4-yl]ureido]-  
thiazole-4-carboxylate**

10

2-(4-Pyridinyl)-4-thiazolcarbonylazide (420 mg, 1.8 mmol) in dry toluene (20 mL) was heated to 85°C under  $N_2$  and maintained at this temperature for 5 min. A solution of 2-amino-4-thiazolcarboxylic acid ethyl ester (350 mg, 2.0 mmol) was added and the resulting mixture was heated at 85°C for 15 h. After cooling to RT, a precipitate formed and was filtered to give the desired compound as a yellow solid. MS  $m/z$ : 376.0 (M+H). Calc'd for  $C_{15}H_{13}N_5O_3S_2$ : 375.05.

20

Example 224

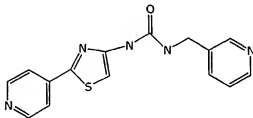
25

**1-(4-Cyclohexylthiazol-2-yl)-3-[2-(pyridin-4-yl)-  
thiazol-4-yl]urea**

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2-(4-Pyridinyl)-4-thiazolcarbonylazide (200 mg, 0.87 mmol) in dry toluene (10 mL) was heated to 85°C under N<sub>2</sub> and maintained at this temperature for 5 min. A solution of 2-amino-4-cyclohexylthiazole (158 mg, 0.87 mmol) was added and the resulting mixture was heated at 85°C for 15 h. After cooling to RT, a precipitate formed and was filtered to give the desired compound as a yellow solid. MS m/z: 386.0 (M+H). Calc'd for C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>OS<sub>2</sub>: 385.10.

10

Example 225

15      1-(Pyridin-3-ylmethyl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

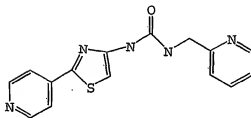
2-(4-Pyridinyl)-4-thiazolcarbonylazide (100 mg, 0.43 mmol) in dry toluene (3 mL) was heated to 105°C under N<sub>2</sub> and maintained at this temperature for 5 min. A solution of 3-(aminomethyl)pyridine (47 mg, 0.43 mmol) in dry toluene (1 mL) was added dropwise via syringe and the resulting mixture heated at 105°C for 2 h. After cooling to RT, solvent was removed under vacuum and the product was purified by silica gel chromatography eluting with MeOH/CH<sub>2</sub>Cl<sub>2</sub> (10%) to give

20

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the desired compound as a light yellow solid. MS m/z:  
312.1 (M+H). Calc'd for  $C_{15}H_{11}N_3OS$ : 311.08.

5

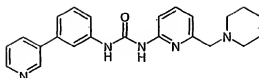
**Example 226**

**1-(Pyridin-2-ylmethyl)-3-(2-(4-pyridin-4-yl-thiazol-4-yl)urea**

10

2-(4-Pyridinyl)-4-thiazolcarbonylazide (100 mg,  
0.43 mmol) in dry toluene (3 mL) was heated to 105 °C  
under nitrogen and maintained at this temperature for 5  
15 min. A solution of 2-(aminomethyl)pyridine (47 mg,  
0.43 mmol) in dry toluene (1 mL) was then added  
dropwise via syringe and the resulting mixture heated  
at 105 °C for 3 h. After cooling to room temperature,  
solvent was removed under vacuum and the product was  
20 purified by silica gel chromatography eluting with  
MeOH/CH<sub>2</sub>Cl<sub>2</sub> (10%) to give a light yellow solid. MS  
m/z: 312.1 (M+H). Calc'd for  $C_{15}H_{11}N_3OS$ : 311.08.

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Example 227

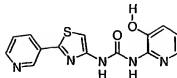
5

**1-[6-(Piperidin-1-ylmethyl)pyridin-2-yl]-3-(3-pyridin-3-yl-phenyl)urea**

- 10 To a stirred solution of phosgene (0.35 mL, 0.65 mmol, 20% in toluene) in dry THF (5 mL) was added 3-(3-pyrid-1-yl)-1-aminobenzene (85 mg, 0.5 mmol) dropwise via the addition funnel. After stirring for 10 min., isopropylethylamine (0.26 mL, 2.0 mmol) was added. The
- 15 resulting mixture was stirred at RT under N<sub>2</sub> for 30 min. 2-Amino-6-piperidinylmethylpyridine (96 mg, 0.5 mmol) in dry THF (5 mL) was added dropwise into the reaction mixture via the addition funnel. The
- 20 resulting mixture was stirred at RT for 15 h. Solvent was removed to give a dark brown liquid which was purified by chromatography on silica gel. Elution with CH<sub>2</sub>Cl<sub>2</sub>:MeOH mixture (95:5) gave the final compound as a pale yellow solid. MS m/z: 387.9 (M<sup>+</sup>). Calc'd. for C<sub>23</sub>H<sub>25</sub>N<sub>5</sub>O - 387.49.

25

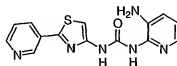
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Example 228

5    1-(3-Hydroxy-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)-urea

TEA (0.27 mL, 1.94 mmol) was added to a solution of 2-(pyridin-3-yl)thiazole-4-carboxylic acid (200 mg, 10 0.97 mmol) and 4A molecular sieves in THF (25 mL) under N<sub>2</sub> at RT. (PhO)<sub>2</sub>PON<sub>3</sub> (0.33 mL, 1.55 mmol) followed by 2-amino-6-hydroxypyridine (268 mg, 2.43 mmol) was added and the resulting mixture heated at reflux for 12 h. After cooling to RT, the heterogeneous mixture was 15 decanted to remove the molecular sieves. The precipitate was collected, rinsing with EtOAc to give a white solid. MS m/z: 313.0 (M+H). Calc'd for C<sub>14</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>S - 313.34.

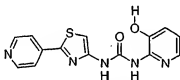
20

Example 229

25    1-(3-Amino-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)-urea

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TEA (0.27 mL, 1.94 mmol) was added to a solution of 2-(pyridin-3-yl)thiazole-4-carboxylic acid (200 mg, 0.97 mmol) and 4A molecular sieves in THF (25 mL) under N<sub>2</sub> at RT. (PhO)<sub>2</sub>PON<sub>3</sub> (0.33 mL, 1.55 mmol) followed by  
5 2-amino-3-aminomethylpyridine (265 mg, 2.43 mmol) was added and the resulting mixture was heated at reflux for 12 h. After cooling to RT, the heterogeneous mixture was decanted to remove the molecular sieves. The precipitate was collected and discarded. The  
10 filtrate was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5) to give a white solid. MS m/z: 313.8 (M+H). Calc'd for C<sub>14</sub>H<sub>12</sub>N<sub>6</sub>OS - 312.36.

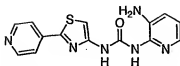
**Example 230**

15

1-(3-Hydroxy-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (200 mg, 0.86  
20 mmol) and 2-amino-3-hydroxymethylpyridine (95 mg, 0.86 mmol) in dry toluene (10 mL) were heated at 100°C for 12 h to give a pale yellow solid which was recrystallized from CHCl<sub>3</sub>/MeOH (99:5) to give a pale yellow solid. MS m/z: 314.0 (M+H). Calc'd for  
25 C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>O<sub>2</sub>S - 313.34.

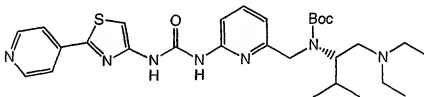
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Example 231

5     **1-(3-Amino-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

2-(4-Pyridinyl)-4-thiazolcarbonylazide (200 mg, 0.86 mmol) and 2-amino-3-aminomethylpyridine (94 mg, 0.86 mmol) in dry toluene (10 mL) were heated at 100°C for 12 h to give a pale yellow solid which was recrystallized from CHCl<sub>3</sub>/MeOH (99:5) to give a pale yellow solid. MS m/z: 313.0 (M+H). Calc'd for C<sub>14</sub>H<sub>12</sub>N<sub>6</sub>OS - 312.36.

15

Example 232

20     **(1-Diethylaminomethyl-2-methyl-propyl)-(6-[3-(2-pyridin-4-yl)-thiazol-4-yl]-ureido)-pyridin-2-ylmethyl-1-carbamic acid tert-butyl ester**

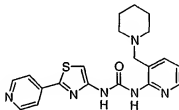
To a stirred solution of N-[(6-amino-(2-pyridyl))-methyl]-N-{1-[(diethylamino)methyl]-2-methylpropyl)-(tert-butoxy)carboxamide (6 mg, 0.016 mmol) in toluene (5 mL) was added 6-(piperidylmethyl)-2-pyridylamine

25

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(0.004 g, 0.016 mmol). The resulting green solution was heated at reflux in a Dean-Stark trap for 1.5 h until the starting materials were consumed. The mixture was brought to RT, concentrated by rotary evaporation and the residue obtained was partitioned between H<sub>2</sub>O (10 mL) and CHCl<sub>3</sub> (35 mL). The organic phase was separated and the aqueous phase was extracted with CHCl<sub>3</sub> (3x10mL). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered, concentrated by rotary evaporation and purified by prep TLC (5:95 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford (1-diethylaminomethyl-2-methyl-propyl)-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl)-carbamic acid tert-butyl ester as an off-white solid. EI-MS m/z 568 (M+H). Calc'd for C<sub>29</sub>H<sub>41</sub>N<sub>7</sub>O<sub>3</sub>S: 567.30.

15

Example 233

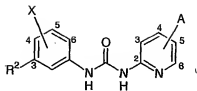
20 1-(3-(Piperidin-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

MS m/z: 395 (M+H).

25 Other compounds included in this invention are set forth in Tables 1-7 below.

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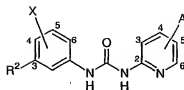
Table 1.



5	#	R <sup>2</sup>	A	X
	234.	4-CH <sub>3</sub> O-phenyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	235.	4-HO-phenyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	236.	3-pyridyl	H	H
	237.	3-pyridyl	6-diethylamino	H
10	238.	3-pyridyl	6-ethyl	H
	239.	4-pyridyl	H	H
	240.	3-HO-phenyl	6-(4-morpholino)	H
	241.	3-NH <sub>2</sub> SO <sub>2</sub> -phenyl	6-(1-piperidinyl)	H
	242.	4-NH <sub>2</sub> SO <sub>2</sub> -phenyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
15	243.	3-NH <sub>2</sub> SO <sub>2</sub> -phenyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	244.	3-NH <sub>2</sub> SO <sub>2</sub> -phenyl	6-(N,N-diethylaminomethyl)	H
	245.	4-(CF <sub>3</sub> CONH <sub>2</sub> SO <sub>2</sub> )phenyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	246.	3-(phenylSO <sub>2</sub> NH)phenyl	6-(1-piperidinyl)	H
20	247.	3-aminophenyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	248.	4-F-phenyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	249.	4-pyridyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	250.	4-pyridyl	6-methyl	H
	251.	4-pyridyl	6-methyl	6-fluoro
25	252.	4-pyridyl	6-ethyl	6-hydroxy
	253.	4-pyridyl	6-ethyl	6-fluoro
	254.	4-pyridyl	6-propyl	6-fluoro
	255.	4-pyridyl	6-propyl	6-hydroxy
	256.	2-pyrazinyl	5-methyl	6-fluoro
30	257.	2-pyrazinyl	4-ethyl	6-hydroxy
	258.	2-pyrazinyl	4-ethyl	6-fluoro
	259.	2-pyrazinyl	6-propyl	H

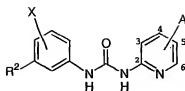
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Table 1. cont.



5	#	R <sup>2</sup>	A	X
	260.	2-pyrazinyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	261.	2-pyrazinyl	6-propyl	6-fluoro
	262.	2-pyrazinyl	6-propyl	6-hydroxy
	263.	5-pyrimidinyl	5-methyl	6-fluoro
10	264.	5-pyrimidinyl	4-ethyl	6-hydroxy
	265.	5-pyrimidinyl	6-ethyl	6-fluoro
	266.	5-pyrimidinyl	6-propyl	H
	267.	5-pyrimidinyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	268.	5-pyrimidinyl	6-propyl	6-fluoro
15	269.	5-pyrimidinyl	6-propyl	6-hydroxy
	270.	2-pyrimidinyl	6-methyl	6-fluoro
	271.	2-pyrimidinyl	6-ethyl	6-hydroxy
	272.	2-pyrimidinyl	6-ethyl	6-fluoro
	273.	2-pyrimidinyl	6-propyl	H
20	274.	2-pyrimidinyl	6-fluoro	H
	275.	2-pyrimidinyl	6-hydroxy	H
	276.	2-pyrimidinyl	4-NH <sub>2</sub> SO <sub>2</sub> phenyl	H
	277.	4-pyridyl	6-ethyl	6-amino
	278.	4-pyridyl	6-propyl	6-amino
25	279.	4-pyridyl	6-methyl	6-amino
	280.	2-pyrazinyl	5-methyl	6-amino
	281.	2-thiazolyl	6-(4-CH <sub>3</sub> -piperazin-1-yl)	H
	282.	4-CH <sub>3</sub> -piperazin-1-yl	6-ethyl	H
	283.	4-morpholinyl	6-ethyl	H
30	284.	3-pyridyl	N,N-diethylaminomethyl	H
	285.	3-pyridyl	1-piperidinylmethyl	H

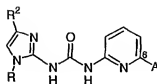
Table 1. cont.



5				
	#	R <sup>2</sup>	A	X
	286.	3-pyridyl	6-(4-morpholinylmethyl)	H
	287.	3-pyridyl	5-(4-morpholinylmethyl)	H
	288.	2-(NH <sub>2</sub> )-5-pyridyl	N,N-diethylaminomethyl	H
10	289.	2-(CF <sub>3</sub> CONH)-5-pyridyl	N,N-diethylaminomethyl	H

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Table 2.

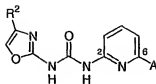


#	R <sup>2</sup>	A	R
290.	3-pyridyl	H	H
291.	4-pyridyl	H	methyl
10	292. 4-pyridyl	H	H
293. 4-pyridyl	methyl	H	H
294. 4-pyridyl	ethyl	H	H
295. 4-pyridyl	propyl	H	H
296. 4-pyridyl	propyl	H	H
15	297. 4-pyridyl	propyl	H
298. 4-pyridyl	morpholino	H	H
299. 4-pyridyl	piperdiny	H	H
300. 4-pyridyl	4-methylpiperazin-1-yl	H	H

20

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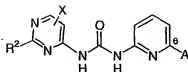
Table 3.



5	#	R <sup>2</sup>	A
	301.	3-pyridyl	H
	302.	4-pyridyl	H
10	303.	4-pyridyl	methyl
	304.	4-pyridyl	ethyl
	305.	4-pyridyl	propyl
	306.	4-pyridyl	propyl
	307.	4-pyridyl	propyl
15	308.	4-pyridyl	morpholino
	309.	4-pyridyl	piperdiny
	310.	4-pyridyl	4-methylpiperazin-1-yl

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Table 4.

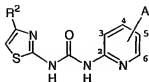


5	#	R <sup>2</sup>	A	X
	311.	3-pyridyl	H	H
	312.	4-pyridyl	H	H
	313.	4-pyridyl	methyl	H
10	314.	4-pyridyl	ethyl	H
	315.	4-pyridyl	propyl	H
	316.	4-pyridyl	propyl	5-F
	317.	4-pyridyl	propyl	5-OH
	318.	4-pyridyl	propyl	5-methoxy
15	319.	4-pyridyl	propyl	5-phenoxy
	320.	4-pyridyl	propyl	5-methylamino
	321.	4-pyridyl	4-morpholino	H
	322.	4-pyridyl	1-piperdiny1	H
	323.	4-pyridyl	4-CH <sub>3</sub> -piperazin-1-yl	H

20

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Table 5.

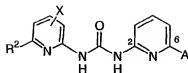


5	#	R <sup>2</sup>	A
	324.	4-pyridyl	6-phenylamino
	325.	4-pyridyl	6-(CH <sub>2</sub> ) <sub>2</sub> NH(CH <sub>2</sub> ) <sub>2</sub> -NH-
	326.	1-sulfonamidylpiperid-4-yl	H
10	327.	1-cyclohexenyl	ethyl
	328.	1-cyclopentenyl	6-(4-CH <sub>2</sub> piperazin-1-yl)
	329.	1-cyclopentenyl	6-diethylaminomethyl
	330.	cyclopropylethynyl	pyrrolidinylmethyl

15

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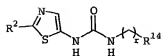
Table 6.



5	#	R <sup>2</sup>	A	X
	331.	3-pyridyl	H	H
	332.	4-pyridyl	H	H
	333.	4-pyridyl	methyl	H
10	334.	4-pyridyl	ethyl	H
	335.	4-pyridyl	propyl	H
	336.	4-pyridyl	propyl	5-F
	337.	4-pyridyl	propyl	5-OH
	338.	4-pyridyl	propyl	5-methoxy
15	339.	4-pyridyl	propyl	5-phenoxy
	340.	4-pyridyl	propyl	5-CH <sub>3</sub> NH-
	341.	4-pyridyl	morpholino	H
	342.	4-pyridyl	piperdiny1	H
	343.	4-pyridyl	4-CH <sub>3</sub> -piperazin-1-yl	H
20	344.	4-morpholinyl	4-morpholinyl	H
	345.	ethyl	ethyl	

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Table 7.



5	#	$R^2$	$R^{14}$	r
	346.	4-pyridyl	4-morpholinyl	3

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The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and their salts. The compounds of examples 1 to 35 exhibited cdk2/cyclin kinase activity with  $IC_{50}$  values less than 50  $\mu M$ . The compounds of examples 1 to 35 exhibited cdk5/cyclin kinase activity with  $IC_{50}$  values less than 50  $\mu M$ . Example 36 exhibited KDR activity with an  $IC_{50}$  value less than 50  $\mu M$ .

#### BIOLOGICAL EVALUATION

##### 15 PROTOCOLS FOR CYCLIN E2/CDK2

###### Cloning of Cdk2 and cyclin 2/Generation of Cdk2 and cyclin 2 Recombinant Baculovirus

The following oligonucleotide primers flanking the coding sequence of the human Cdk2 cDNA clone were used to amplify the gene and place EcoRI and HindIII restriction sites at the 5' and 3' ends of the gene respectively. [5' oligo-5'-AAGCGCGCGGAATTCATAAATATGGAGAAGTCCAAAAGGTGGAA-3'; 3' oligo-5'-CTCGACAAGCTTATTAGAGTCGAAGATGGGGTAC-3']

The following oligonucleotide primers flanking the coding sequence of the human CycE2 cDNA clone were used to amplify the gene and place XhoI and SphI restriction sites at the 5' and 3' ends of the gene respectively. A His tag was also placed at the N-terminus of the CycE2 protein. [5' oligo-5'-CCCGGGATCTCGAGATAAATATGCATCATCATCATTCATCAAGACGAAGTAGCCG

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TTTACAA -3'; 3' oligo-5'-

CCCCGTACCGCATGCTTAGTGTTTCTCGGTGGTTTTTC -3']

- 5 CycE-2 and Cdk2 PCR fragments were subcloned into the vector pFastBacDual (Gibco/LifeTechnologies) using the restriction sites indicated above. Recombinant virus was made following protocols supplied by the manufacturer.

10 Expression of cyclin 2/CDK2 in insect cells

- Hi5 cells were grown to a cell density of  $1 \times 10^6$  cells per ml in 800 ml of Excell 405 media (JRH). Cells were infected with virus at a multiplicity of 1. Infected cultures were incubated with shaking at 28°C.
- 15 Cells were harvested by centrifugation.

Cloning of Cdk5 and p25/Generation of CDK5 and p25  
Recombinant Baculovirus

- Based on the reported sequences of human CDK5 and p35, GenBank accession numbers X66364 and X80343 respectively, oligonucleotide primers flanking the coding sequence of each gene were used to amplify CDK5 (5'-GCGATGCAGAAATACGAGAAACT-3'; 5'-CCCCACTGTCTCACCCCTCTCAA-3') and p35 (5'-CGGTGAGCGGTTTATCCC-TCC-3'; 5'-GCATTGAATCCTTGAGCCATGACG-3') from a human fetal brain cDNA library (Clontech). p25, a C-terminal proteolytic fragment corresponding to amino acids 99-307 of full-length p35 (Lew, et. al), was PCR subcloned from the
- 30 p35 sequence using oligonucleotide primers (5'-CGGGATCCATGGCCCGCCCCACCGGCCCA-3'; 5'-

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CCAAGCTTTCACCGATCCAGGCCTAG-3'). The p25 PCR product (629bp) was cloned into the pFastBacHTb baculovirus expression vector (Gibco BRL) using *Bam*HI and *Hind*III. CDK5 was PCR subcloned using oligonucleotide primers

5 (5'-CGGGATCC -GCCACCATGCAGAAATACGAGAACTGG-3'; 5'-GGACTAGTCTAGGGCGGAC-AGAAGTCG-3'). The CDK5 PCR product (879 bp) was cloned into the pFastBac1 baculovirus expression vector (Gibco BRL) using *Bam*HI and *Spe*I. Recombinant baculovirus expressing human Cdk5 and N-

10 terminally six histidine tagged p25 were generated using the Bac-to-Bac system (Gibco BRL).

#### Expression of P25/CDK5 in insect cells

Coinfections of Hi5 cells by recombinant

15 baculovirus containing the P25 gene and another containing the CDK5 gene were done at a multiplicity of infection of 5 (each virus). The Hi5 cultures were set to a cell concentration of  $1 \times 10^6$  cells per ml in 800 ml of Excell media by JRH. The cultures were grown in

20 2.6L fernbach flasks with shaking (110 rpm) at 27°C for 60 hours. The cells were harvested by centrifugation.

#### Purification of complexes

All steps were performed at 4°C. Insect cells

25 expressing either cyclin E2/CDK2 or p25/CDK5 were lysed using a microfluidizer (Microfluidics Corporation.) The lysis buffer contained 10mM Hepes, 150mM NaCl, 20mM MgCl<sub>2</sub>, 20mM imidazole, 0.5mM EDTA, 10% glycerol, 25µg/ml Aprotinin, 25µg/ml Leupeptin, 1mM Pefabloc, pH 7.5).

30 Total protein was determined on the resulting lysate using the Bradford method with a BSA standard curve. Protamine sulfate was added to the lysate to give a

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- final 30:1 protein:protamine sulfate, incubated for 15-20 minutes and centrifuged at 14000xg for 30 minutes to remove insoluble material. Ni-NTA superflow resin (Qiagen Inc) was equilibrated in lysis buffer and
- 5 incubated with the centrifugation supernatant for 1 hour while rotating. The slurry was packed in a glass column and washed until a stable UV baseline was reached. Proteins were eluted with a linear gradient of 20-300mM imidazole over 15 column volumes.
- 10 Fractions were analyzed by SDS-PAGE and Western blot. Appropriate fractions were pooled, total protein determined, and submitted for kinase assay.

#### CDK2 Kinase Assay

- 15 CDK2 kinase assays were carried out with inhibitor (dissolved in DMSO) in a total volume of 50  $\mu$ l with 1nM enzyme (His-tagged cyclin 2/CDK2), 1  $\mu$ M Histone-H1 (Gibco), 25  $\mu$ M ATP, 20  $\mu$ Ci/ml  $^{33}$ P-ATP (Amersham; 2500 Ci/mmmole) in kinase buffer (50 mM Tris-HCl, pH 7.5, 5
- 20 mM MgCl<sub>2</sub>, 1 mM EGTA, 5 mM DTT, 200  $\mu$ g/ml BSA and 20 mM  $\beta$ -glycerophosphate for 60 minutes at 25 °C. Reactions were stopped by the addition of an equal volume of 30% trichloroacetic acid (Sigma). Precipitates were formed by incubation at 4 °C for 60 minutes and then collected
- 25 by filtration on Millipore® filter plates (MAFC NOB10). Forty microliters of MicroScint-20 (Packard) was added, and then were counted on a Packard TopCount®. Raw cpms were analyzed with a four-parameter logistic fit using the Levenburg Marquardt algorithm (Xlfit software IDBS
- 30 LTD). Kinetic parameters were calculated by non-linear regression analysis using Grafit (Erithacus Software LTD). Riscovotine (BIOMOL Research Labs Inc., Plymouth

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Meeting, PA.) and staurosporin (Sigma, St. Louis MO) were used as standards.

#### CDK5 Kinase Assay

- 5 CDK5 kinase assays were carried out with inhibitor (dissolved in DMSO) in a total volume of 50  $\mu$ l with 1nM enzyme (His-tagged p25/CDK5), 1  $\mu$ M Histone-H1 (Gibco), 25  $\mu$ M ATP, 20  $\mu$ Ci/ml  $^{33}$ P-ATP (Amersham; 2500 Ci/mmol) in kinase buffer (50 mM Tris-HCl, pH 7.5, 5 mM MgCl<sub>2</sub>, 1  
10 mM EGTA, 5 mM DTT, 200  $\mu$ g/ml bovine serum albumin and 20 mM  $\beta$ -glycerophosphate) for 60 minutes at 25°C. Reactions were stopped by the addition of an equal volume of 30% trichloroacetic acid (Sigma). Precipitates were formed by incubation at 4 °C for 60  
15 minutes and then collected by filtration on Millipore® filter plates (MAFC NOB10). Forty microliters of MicroScint-20 (Packard) was added, and then were counted on a Packard TopCount®. Raw cps were analyzed with a four-parameter logistic fit using the Levenburg  
20 Marquardt algorithm (Xlfit software IDBS LTD). Kinetic parameters were calculated by non-linear regression analysis using Grafit (Erithacus Software LTD). Riscovitine (BIOMOL Research Labs Inc., Plymouth Meeting, PA.) and staurosporin (Sigma, St. Louis MO)  
25 were used as standards.

#### **KDR Assay**

- KDR kinase assays were carried out in Polypro 96  
30 well clear round bottom plates (Costar). An aqueous kinase reaction buffer was prepared (100 mM Tris-HCl,

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125 mM  $MgCl_2$ , 25 mM  $MnCl_2$ , 2 mM EGTA, 0.25 mM SOV and 2 mM DTT). To each well buffer (50 $\mu$ l) and biotinylated gastrin peptide substrate (10 $\mu$ l) was added. A pool of KR was diluted (1:10) in buffer. Diluted KDR (10 $\mu$ l) was added to the wells except for the controls. Inhibitor, dissolved in DMSO (5 $\mu$ l) was added and the wells were incubated with shaking for 30 minutes at 25°C. A co-substrate was added (75 mM  $MnCl_2$ , 50  $\mu$ M ATP) (10 $\mu$ L) in one row and the plates were incubated for 60 more minutes with shaking. A portion of the kinase mixture (5 $\mu$ l) was transferred to a Polypro 96 well black bottom plate (costar) containing 40 $\mu$ l TBS (50 mM Tris-HCl, 100 mM NaCl, 0.1% BSA and 0.05% Tween 20), 20  $\mu$ l 1:200 dilution streptavidin-AFC and 20 $\mu$ l 0.45 nM Eu-PT66. The plates were incubated for 30 minutes with shaking then read on a Discovery homogenous time resolved fluorescence (HTRF) analyzer (Wallac). Staurosporin (Sigma) was used as a standard. Kinetic parameters were calculated using Excelfit software.

20

#### CELL PROLIFERATION ASSAY

Cell proliferation was measured using a colorimetric immunoassay (B/M Roche #164 7229), based on the measurement of pyrimidine analog BrdU incorporation during DNA synthesis in proliferating cells. Cells, e.g., human PC-3 prostate carcinoma cells, huFSF normal human foreskin fibroblast cells, HCT 116 human colon carcinoma cells or HT 29 human colon carcinoma cells, were cultured in a 96-well plate for 24 hours, until a cell count of  $3 \times 10^3$  to  $6 \times 10^3$  cells per well in duplicate wells were achieved, in a

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well volume of 200  $\mu$ l. The media was changed and 1  $\mu$ l of 200X control inhibitors or compounds was added to each well. Cells are incubated for 48 hours at 37°C. The cells were labeled with BrdU for 4 hours at 37°C.

5 The labeling medium was removed and in one step, the cells were fixed and the DNA was denatured (30 minutes at room temperature). Anti-BrdU-POD antibody was added to bind to the BrdU incorporated in newly synthesized cellular DNA (60-90 minutes at room temperature). The

10 cells were washed 3X with washing buffer, substrate (100 $\mu$ l) was added and the cells were incubated for 10 minutes at room temperature. The substrate reaction was stopped by adding H<sub>2</sub>SO<sub>4</sub> (25 $\mu$ l of 1M H<sub>2</sub>SO<sub>4</sub>). The amount of BrdU incorporated was quantified by measuring

15 the absorbance at 450 nm using ELISA reader. IC<sub>50</sub>'s were calculated using GraFit (Sigma).

**ISCHEMIC STROKE MODEL: MIDDLE CEREBRAL ARTERY OCCLUSION  
(MCAO) IN VIVO**

20 The compounds' effect on treating stroke was measured in a MCAO rat model. (L. Belayev et al., Stroke, 27, 1616-23 (1996). Male Sprague-Dawley rats (300-330g body weight) were anesthetized with halothane

25 and MCAO was induced by inserting a poly-L-lysine coated monofilament suture to the beginning of the middle cerebral artery (MCA). After various time points (60, 90 or 120 min), the intraluminal suture was carefully removed to start reperfusion. Physiological

30 conditions (blood O<sub>2</sub>, CO<sub>2</sub>, pH, glucose, blood pressure) were monitored and kept stable during the surgery. The

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compound was dissolved in 20% Captisol in phosphate buffered saline and administered (orally, IV or IP) 90 minutes after ischemia onset, at the beginning of reperfusion. Further dosing occurred at 4-8 hours and  
5 twice a day thereafter.

The use of behavioral tests was directly analogous to the clinical neurological examination for assessing ischemic deficits and rates of behavioral recovery. The battery consisted of four tests: (1) postural reflex  
10 test, (2) forelimb placing test (JB Bederson et al., Stroke, 17:472-76 (1986) (L. Belayev et al., Stroke, 26:2313-20 (1995), (3) contralateral foot fault index (A. Tamura et al., J. Cereb Blood Flow Metab., 1:53-60 (1981) (DM Freeney, Science, 217:855-57 (1982), and (4)  
15 cylinder asymmetry (TA Jones and T. Schallert, J. Neurosci., 14:2140-52 (1994). Tests were performed once a day for three days and then once a week for a period of 30 days. These tests are useful in assessing neurological deficits for short-term studies; the  
20 cylinder asymmetry test appeared to be the most useful for long term experiments.

At the end of the experiment, the infarct volume was measured (JB Bederson et al., Stroke, 17:1304-8 (1986) (KA Osborne et al, J. Neurol Neurosurg.  
25 Psychiatry, 50:402 (1987) (RA Swanson et al., J. Cereb. Blood Flow Metab., 10:290-3 (1990). The brains were removed and sliced coronally at 1 mm thickness. The brain slices were stained with 2% (w/vol) 2,3,5-triphenyltetrazolium chloride (TTC) which stains the  
30 infarcted areas of the brain in white and allows for the measurement of infarct volume by an image-analysis

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system. Edema volume that contributes to infarct volume was subtracted by comparison with the total volume of the contralateral hemisphere. Example 14 and 43 significantly (~30%) improved the responses in the behavioral tests and reduced the brain infarct volume after 2-3 days at doses of 10-30 mg/kg.

### Formulations

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of Formula I in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal

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agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a  
5 tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may  
10 contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other  
15 factors, but, once again, can be determined using routine methods.

The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of  
20 this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed.  
25 Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg body weight, preferably between about 0.5 and about 50 mg/kg body weight and most preferably between about 0.1 to 20  
30 mg/kg body weight, may be appropriate may be

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appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g.,

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from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

- 5           When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of  
10 the cream base may include, for example at Least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which  
15 enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

- The compounds of this invention can also be  
20 administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the  
25 reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered  
30 to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

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The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one  
5 emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s)  
10 with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers.  
15 suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

20 The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream  
25 should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol  
30 diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-

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ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white  
5 soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable  
10 carrier, especially an aqueous solvent for the active ingredients. The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

15 Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents  
20 mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil,  
25 sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with  
30 suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie.Captisol), cosolvent

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solubilization (ie. propylene glycol) or micellar solubilization (ie. tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings.

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Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

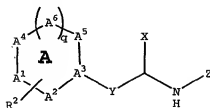
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

All mentioned references, patents, applications and publications, are hereby incorporated by reference in their entirety, as if here written.

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WHAT IS CLAIMED IS:

1. A compound of formula I



I

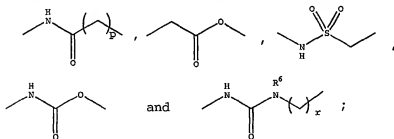
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wherein each of A<sup>1</sup>-A<sup>6</sup> is selected from CH<sub>2</sub>, CH, C, O, S, NH and N; wherein A<sup>1</sup>-A<sup>6</sup> together form a ring A selected from

- 10 additionally substituted or unsubstituted 5- or 6-membered heterocyclyl,  
 additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group,  
 additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, and  
 15 additionally substituted or unsubstituted phenyl,  
 wherein the ring A is additionally substituted with one or more substituents independently selected from halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>,  
 20 cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted phenyl, lower alkyl, cyano, lower hydroxyalkyl,  
 25 nitro, lower alkenyl, lower alkynyl and lower haloalkyl;
- wherein X and Z taken together form a nitrogen containing ring selected from

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- unsubstituted 5-6 membered heterocyclyl,  
 unsubstituted 5-6 membered heterocyclyl fused with a  
 phenyl group,  
 5-6 membered heterocyclyl substituted with one or  
 5 more substituents independently selected from  $R^1$ ,  
 and  
 5-6 membered nitrogen-containing heterocyclyl, fused  
 with a phenyl group, substituted with one or more  
 substituents independently selected from  $R^1$ ;  
 10 wherein  $R^1$  is independently selected from H, halo, -  
 $OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-CONR^3R^3$ ,  $-NR^3R^3$ ,  
 $-C(S)NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-NR^3C(O)R^3$ ,  
 cycloalkyl, optionally substituted phenylalkylenyl,  
 optionally substituted 4-10 membered heterocyclyl,  
 15 optionally substituted 4-10 membered  
 heterocyclylalkyl, optionally substituted phenyl,  
 optionally substituted phenoxy, lower alkyl, lower  
 cyano, lower alkenyl, lower alkynyl and lower  
 haloalkyl;  
 20 wherein Y is selected from, in either orientation,



- wherein  $R^2$  is selected from  
 lower alkylaminoalkynyl,  
 25 cycloalkenyl- $C_{2-3}$ -alkynyl,  
 cycloalkyl- $C_{2-3}$ -alkynyl,  
 phenyl- $C_{2-3}$ -alkynyl,

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5-6 membered heterocyclyl-C<sub>2-3</sub>-alkynyl,  
substituted or unsubstituted cycloalkenyl,  
substituted or unsubstituted phenyl,  
substituted or unsubstituted 5-6 membered  
5 heterocyclyl, and  
substituted or unsubstituted 5-6 membered  
heterocyclyl bridged with a phenyl group;  
wherein substituted R<sup>2</sup> is substituted with one or  
more substituents independently selected from  
10 halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -  
NR<sup>3</sup>R<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -  
NHC(O)R<sup>3</sup>, -SO<sub>2</sub>NHC(O)R<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, nitro,  
cycloalkyl, optionally substituted  
phenylalkylenyl, optionally substituted 4-7  
15 membered heterocyclyl, optionally substituted  
heterocyclylalkylenyl, optionally substituted  
phenyl, optionally substituted  
phenoxyalkylenyl, optionally substituted  
heterocycliloxyalkyl, lower alkyl, cyano, lower  
20 hydroxyalkyl, lower alkoxyalkyl, lower  
azidoalkyl, lower aminoalkyl, lower  
(hydroxyalkyl)aminoalkyl, lower  
alkylaminoalkyl, lower alkylaminoalkoxy, lower  
aminoalkoxyalkyl, lower (alkylaminoalkyl)amino  
25 lower ((alkylamino)alkylamino)alkyl, lower  
alkylaminoalkylaminocarbonyl, lower cyanoalkyl,  
lower alkenyl, lower alkynyl and lower  
haloalkyl;  
wherein R<sup>3</sup> is selected from H, lower alkyl, optionally  
30 substituted phenyl, optionally substituted  
phenylalkyl, optionally substituted heterocyclyl,

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optionally substituted heterocyclylalkyl, C<sub>3</sub>-C<sub>6</sub>  
cycloalkyl, and lower haloalkyl;  
wherein R<sup>6</sup> is selected from H, alkyl, 5-6 membered  
heterocyclylalkylenyl and alkylamino;

5 wherein p is 1 or 2;

wherein q is 0 or 1; and

wherein r is 0-3;

and pharmaceutically acceptable salts thereof;

provided A is not thiazol-2-yl when Y is ureido;

10 further provided A is not phenyl when R<sup>2</sup> is pyridyl  
or pyrimidyl when Y is ureido and when X and Z taken  
together form 1-methylindolyl; further provided A is  
not 1-phenylpyrazol-4-yl when Y is ureido when X and  
Z taken together form pyrazolyl and when R<sup>2</sup> is

15 pyrrol-1-yl; further provided A is not 5-  
methylpyrazol-3-yl when Y is ureido when X and Z  
taken together form pyrazolyl and when R<sup>2</sup> is phenyl;  
further provided A is not thiazolyl or  
dihydrothiazolyl when R<sup>2</sup> is indolyl when Y is ureido

20 and when X and Z taken together form thiazolyl or  
dihydrothiazolyl; further provided A is not  
pyrazolyl or dihydropyrazolyl when R<sup>2</sup> is 2-furyl  
when Y is ureido and when X and Z taken together  
form thiazolyl or dihydrothiazolyl when R<sup>1</sup> is

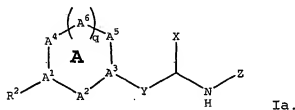
25 isopropyl; further provided A is not oxadiazolyl or  
dihydrooxadiazolyl when R<sup>2</sup> is phenyl when Y is  
ureido and when X and Z taken together form  
thiazolyl or dihydrothiazolyl when R<sup>1</sup> is isopropyl;

provided A is not thiazolyl when R<sup>2</sup> is 3-pyridyl  
30 when Y is ureido and when X and Z taken together  
form 2-(3-pyridyl)thiazol-4-yl; and further provided

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A is not thien-3-yl when Y is ureido when X and Z taken together form thienyl and when R<sup>2</sup> is pyrrol-1-yl.

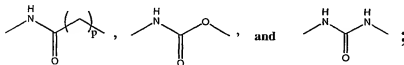
- 5            2. Compound of Claim 1 and pharmaceutically acceptable salts thereof, of formula Ia



- 10           3. Compound of Claim 2, and pharmaceutically acceptable salts thereof, wherein A is selected from 5- or 6- membered heterocyclyl.

4. Compound of Claim 3, and pharmaceutically acceptable salts thereof, wherein A is selected from 5- or 6- membered heteroaryl.

5. Compound of Claim 4, and pharmaceutically acceptable salts thereof, wherein A is selected from  
20    thiazolyl, oxazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl; wherein Y, in either orientation is selected from



- 25    wherein p is 1-2;

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wherein X and Z taken together form a ring selected from

substituted or unsubstituted 5-6 membered nitrogen-containing heteroaryl, and

- 5 substituted or unsubstituted 5-6 membered nitrogen-containing heteroaryl fused with a phenyl group; and

wherein R<sup>2</sup> is selected from

substituted phenyl,

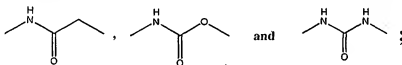
- 10 substituted or unsubstituted 5-6 membered nitrogen-containing heteroaryl, and

substituted or unsubstituted 5-6 membered nitrogen-containing heteroaryl fused with a phenyl group.

- 15 6. Compound of Claim 5, and pharmaceutically acceptable salts thereof,

wherein A is selected from thiazolyl, oxazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl;

- 20 wherein Y, in either orientation is selected from



wherein X and Z taken together form a ring selected

from substituted or unsubstituted thiazolyl,

- 25 pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl,

triazinyl, isoindolyl, indolyl, indazolyl, purinyl,

[1,6]naphthyridinyl, 5,6,7,8-

tetrahydro[1,6]naphthyridinyl, isoquinolyl and

quinolyl; and

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wherein R<sup>2</sup> is substituted phenyl or a substituted or  
unsubstituted heterocyclyl substituent selected from  
thiazolyl, pyridyl, pyrazinyl, pyrimidinyl,  
pyridazinyl, triazinyl, isoindolyl, indolyl,  
5 indazolyl, purinyl, isoquinolyl and quinolyl.

7. Compound of Claim 6, and pharmaceutically  
acceptable salts thereof, wherein A is selected from  
thiazolyl, oxazolyl, and imidazolyl; wherein Y is  
10 ureido; wherein X and Z taken together form a ring  
selected from pyridyl, pyrazinyl, pyrimidinyl,  
pyridazinyl, [1,6]naphthyridinyl and 5,6,7,8-  
tetrahydro[1,6]naphthyridinyl; wherein R<sup>1</sup> is  
independently selected from optionally substituted  
15 pyrrolidinyl, optionally substituted piperazinyl,  
optionally substituted piperidinyl, morpholinyl,  
optionally substituted pyridyl, 1,4-dioxo-8-aza-  
spiro[4.5]decyl, optionally substituted phenyl, C<sub>1</sub>-C<sub>4</sub>  
alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkyl, amino,  
20 C<sub>1</sub>-C<sub>4</sub>-azidoalkyl, C<sub>1</sub>-C<sub>4</sub>-cyanoalkyl, C<sub>1</sub>-C<sub>4</sub>-aminoalkyl,  
hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-  
C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-  
C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-  
C<sub>1</sub>-C<sub>4</sub>-alkyl (optionally substituted pyrrolidinyl)-C<sub>1</sub>-C<sub>2</sub>-  
25 , (optionally substituted piperidinyl)-C<sub>1</sub>-C<sub>2</sub>-,  
(optionally substituted piperazinyl)-C<sub>1</sub>-C<sub>2</sub>-, 4-  
morpholinyl-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted  
imidazolyl)-C<sub>1</sub>-C<sub>2</sub>-, phthalimidylethyl, optionally  
substituted azepanyl-C<sub>1</sub>-C<sub>2</sub>-, 1,4-dioxo-8-aza-  
30 spiro[4.5]decyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted  
pyridyloxy, optionally substituted phenoxy,

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- tetrahydrofuryl-0-, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted phenoxy-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 5-6-membered N-containing heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, aminocarbonyl, C<sub>1</sub>-C<sub>3</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino and C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino; and
- wherein R<sup>2</sup> is selected from phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, purinyl, isoquinolyl and quinolyl, wherein R<sup>2</sup> is unsubstituted or substituted with one or more substituents independently selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, halo, amino, C<sub>1</sub>-C<sub>2</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkoxy-C<sub>1</sub>-C<sub>2</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>2</sub>-alkylthio, cyano, C<sub>1</sub>-C<sub>2</sub>-haloalkyloxy, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylaminocarbonyl, nitro, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylaminosulfonyl, C<sub>1</sub>-C<sub>2</sub>-alkylaminosulfonyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkylaminosulfonyl, phenyl-C<sub>1</sub>-C<sub>2</sub>-alkylaminosulfonyl, (optionally substituted phenyl)aminosulfonyl, piperidinyl, morpholinyl, C<sub>1</sub>-C<sub>2</sub> alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub> alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, aminocarbonyl, C<sub>1</sub>-C<sub>2</sub>-alkylcarbonylamino, morpholinyl-C<sub>1</sub>-

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C<sub>4</sub>-alkylenylamino, C<sub>1</sub>-C<sub>2</sub>-alkylamino and C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino.

8. Compound of Claim 7, and pharmaceutically acceptable salts thereof, wherein X and Z taken together form a ring selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl; wherein R<sup>1</sup> is one or more substituents selected from 3-(N,N-dimethylamino)-1-pyrrolidinyl, 1-methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, piperidinyl, morpholinyl, 4-amino-1-piperidinyl, 4-(N-hydroxyethylamino)-1-piperidinyl, 4-(N-propylamino)-1-piperidinyl, 4-(N-benzylamino)-1-piperidinyl, 4-oxo-piperidinyl, 4-(hydroxyimino)-piperidinyl, 4-morpholinyl, 1,4-dioxo-8-aza-spiro[4.5]decyl, pyridyl, phenyl, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, amino, azidomethyl, hydroxymethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, fluoro, chloro, bromo, aminoethyl, aminomethyl, cyanomethyl, 1-pyrrolidinyl-CH<sub>2</sub>-, 2-methoxycarbonyl-1-pyrrolidinyl-CH<sub>2</sub>-, 2-carboxy-1-pyrrolidinyl-CH<sub>2</sub>-, 2-hydroxymethyl-1-pyrrolidinyl-CH<sub>2</sub>-, 1-piperidinyl-CH<sub>2</sub>-, 4-methyl-1-piperidinyl-CH<sub>2</sub>-, 3-methyl-1-piperidinyl-CH<sub>2</sub>-, 2-methyl-1-piperidinyl-CH<sub>2</sub>-, 3,5-dimethyl-1-piperidinyl-CH<sub>2</sub>-, 4-oxo-1-piperidinyl-CH<sub>2</sub>-, 4-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 3-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 2-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-(1-pyrrolidinyl)-1-

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- piperidinyl-CH<sub>2</sub>-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-propylamino)-1-piperidinyl-CH<sub>2</sub>-, 1-methyl-4-piperazinyl-CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, (2-methyl-1-imidazolyl)-CH<sub>2</sub>-, 3-(N,N-diethylamino)carbonyl-
- 5 1-piperidinyl-CH<sub>2</sub>-, phthalimidylethylenyl, 1-azepanyl-CH<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-CH<sub>2</sub>-, 4-(methyl)phenoxy-methylenyl, 4-(N,N-dimethylaminomethylenyl)phenoxy-methylenyl, methylaminothiocarbonyl, methoxy-methylenyl,
- 10 ethylaminothiocarbonyl, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminoethylenyl, N-methylaminomethylenyl, N-(hydroxypropyl)aminomethylenyl, N-ethylaminomethylenyl, Boc-aminoethoxymethylenyl, aminoethoxymethylenyl, (1-
- 15 aza-bicyclo[2.2.2]oct-3-yl)-oxy, 2-pyrrolidinylmethoxy, 1-methyl-2-pyrrolidinylmethoxy, azetidin-3-ylmethoxy, N-Boc-azetidin-3-ylmethoxy, N-Boc-piperidin-4-ylethoxy, 1-methyl-4-piperidinylethoxy, 4-piperidinylethoxy, 4-piperidinylmethoxy, N,N-dimethylaminoethoxy, 3-
- 20 tetrahydrofuryl-0-, 3-tetrahydrofurylmethoxy, 4-tetrahydrofurylmethoxy, 4-methylphenoxy, 4-(aminoethyl)phenoxy, 4-(1-imidazolyl)phenoxy, 2,4-dimethylphenoxy, phenoxy, 4-cyanophenoxy, 4-[1,3]dioxolan-2-ylphenoxy, 4-fluorophenoxy, 3,4-
- 25 difluorophenoxy, ethoxycarbonyl, morpholinylethylenylaminocarbonyl, morpholinylpropylenylaminocarbonyl, 1-piperidinylcarbonyl, methylaminocarbonyl, ethylaminocarbonyl, N,N-diethylaminocarbonyl, N-(N',N'-
- 30 dimethylaminoethylenyl)aminocarbonyl, aminocarbonyl, morpholinylethylenylamino, morpholinylpropylenylamino,

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N,N-diethylamino, N,N-dimethylamino, N,N-diethylamino(2-propylenyl)aminomethylenyl, N,N-diethylamino(1-propylenyl)aminomethylenyl and N-(N',N'-dimethylaminoethylenyl)amino; and R<sup>2</sup> is selected from

5 pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, wherein R<sup>2</sup> is unsubstituted or substituted with one or more substituents independently selected from chloro, fluoro, amino, methoxy, ethoxy, ethoxymethyl, methylthio, trifluoromethylcarbonylamino and

10 trifluoroethoxy.

9. Compound of Claim 7 wherein R<sup>2</sup> is selected from 3-fluorophenyl, 4-fluorophenyl, 4-(N,N-dimethylamino)phenyl, phenyl, 3-trifluoromethylphenyl,

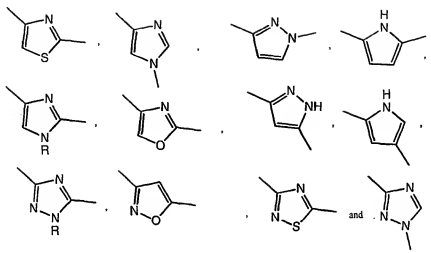
15 4-trifluoromethylphenyl, 4-aminophenyl, 3-aminophenyl, 3-nitrophenyl, 4-(methylcarbonylamino)phenyl, 4-aminosulfonylphenyl, 4-(phenylsulfonylamino)phenyl, 4-(4-morpholinylsulfonyl)phenyl, 4-(trifluoroacetylaminosulfonyl)phenyl, 4-[(4-

20 chlorophenyl)aminosulfonyl]phenyl, 4-hydroxyphenyl, 2,4-difluorophenyl, 2,4-dimethoxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 4-methylthiophenyl, 4-cyanophenyl, 4-trifluoromethoxyphenyl, 4-methoxyphenyl, 3-methoxyphenyl and 2-methoxyphenyl.

25

10. Compound of Claim 3 wherein A is selected from

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wherein R is selected from H, C<sub>1</sub>-C<sub>3</sub> alkyl and  
optionally substituted phenyl;  
and pharmaceutically acceptable salts thereof.

5

11. Compound of Claim 10, and pharmaceutically acceptable salts thereof, wherein X and Z together form pyridyl or substituted pyridyl; wherein R<sup>1</sup> is independently selected from optionally substituted
- 10 pyrrolidinyl, optionally substituted piperazinyl, optionally substituted piperidinyl, morpholinyl, optionally substituted pyridyl, 1,4-dioxo-8-aza-spiro[4.5]decyl, optionally substituted phenyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkyl, amino,
- 15 C<sub>1</sub>-C<sub>4</sub>-azidoalkyl, C<sub>1</sub>-C<sub>4</sub>-cyanoalkyl, C<sub>1</sub>-C<sub>4</sub>-aminoalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl (optionally substituted pyrrolidinyl)-C<sub>1</sub>-C<sub>2</sub>-
- 20 , (optionally substituted piperidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperazinyl)-C<sub>1</sub>-C<sub>2</sub>-, 4-morpholinyl-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted

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- imidazolyl)-C<sub>1</sub>-C<sub>2</sub>-, phthalimidylethyl, optionally substituted azepanyl-C<sub>1</sub>-C<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted pyridyloxy, optionally substituted phenoxy,
- 5 tetrahydrofuryl-0-, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted phenoxy-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-
- 10 C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-
- 15 alkylaminocarbonyl, 5-6-membered N-containing heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, aminocarbonyl, C<sub>1</sub>-C<sub>3</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino and C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino; and wherein R<sup>2</sup> is selected from pyridyl or pyridyl further substituted with one or
- 20 more substituents independently selected from chloro, fluoro, amino, C<sub>1</sub>-C<sub>2</sub> alkoxy, C<sub>1</sub>-C<sub>2</sub> alkoxy-C<sub>1</sub>-C<sub>2</sub>-alkyl, C<sub>1</sub>-C<sub>2</sub>-alkylthio, C<sub>1</sub>-C<sub>2</sub> haloalkylcarbonylamino and trifluoroethoxy.

- 25 12. Compound of Claim 11, and pharmaceutically



acceptable salts thereof, wherein A is

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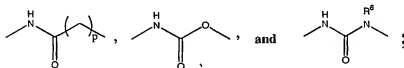
13. Compound of Claim 3, and pharmaceutically acceptable salts thereof, wherein A is 6-membered heteroaryl.

5 14. Compound of Claim 2, and pharmaceutically acceptable salts thereof, wherein A is 5- or 6-membered heteroaryl fused with a phenyl ring.

15 15. Compound of Claim 2, and pharmaceutically acceptable salts thereof, wherein A is phenyl.

16. Compound of Claim 2, and pharmaceutically acceptable salts thereof, wherein A is 5- or 6-membered cycloalkenyl.

15 17. Compound of Claim 2, and pharmaceutically acceptable salts thereof, wherein A is selected from phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, cyclopentadienyl and cyclopentenyl; wherein Y, in  
20 either orientation, is selected from

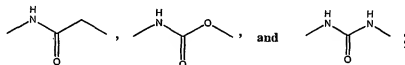


wherein X and Z together form a ring selected from substituted or unsubstituted pyridyl, pyrazinyl,  
25 pyrimidinyl, pyridazinyl, purinyl, isoquinolyl and quinolyl, wherein said ring is optionally substituted with  $\text{R}^1$ ; wherein  $\text{R}^2$  is selected from substituted or unsubstituted phenyl, morpholinyl, piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyrimidinyl,

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pyridazinyl, indolyl, purinyl, isoquinolyl and quinolyl; and wherein R<sup>6</sup> is H.

18. Compound of Claim 17, and pharmaceutically acceptable salts thereof, wherein A is selected from phenyl, pyridyl and pyrimidinyl; wherein Y, in either orientation is selected from



10

- wherein X and Z together form a ring selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, wherein said ring is optionally substituted with R<sup>1</sup>; wherein R<sup>1</sup> is one or more substituents independently selected from 3-(N,N-dimethylamino)-1-pyrrolidinyl, 1-methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, piperidinyl, morpholinyl, 4-amino-1-piperidinyl, 4-(N-hydroxyethylamino)-1-piperidinyl, 4-(N-propylamino)-1-piperidinyl, 4-(N-benzylamino)-1-piperidinyl, 4-oxo-piperidinyl, 4-(hydroxyimino)-piperidinyl, 4-morpholinyl, 1,4-dioxo-8-aza-spiro[4.5]decyl, pyridyl, phenyl, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, amino, azidomethyl, 25 hydroxymethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, fluoro, chloro, bromo, aminoethyl, aminomethyl, cyanomethyl, 1-pyrrolidinyl-CH<sub>2</sub>-, 2-methoxycarbonyl-1-pyrrolidinyl-CH<sub>2</sub>-, 2-carboxy-1-pyrrolidinyl-CH<sub>2</sub>-, 2-hydroxymethyl-1-pyrrolidinyl-CH<sub>2</sub>-,

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- 1-piperidinyl-CH<sub>2</sub>-, 4-methyl-1-piperidinyl-CH<sub>2</sub>-, 3-methyl-1-piperidinyl-CH<sub>2</sub>-, 2-methyl-1-piperidinyl-CH<sub>2</sub>-, 3,5-dimethyl-1-piperidinyl-CH<sub>2</sub>-, 4-oxo-1-piperidinyl-CH<sub>2</sub>-, 4-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 3-hydroxy-1-piperidinyl-CH<sub>2</sub>-,
- 5 piperidinyl-CH<sub>2</sub>-, 2-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH<sub>2</sub>-,
- 10 piperidinyl-CH<sub>2</sub>-, 4-(N-propylamino)-1-piperidinyl-CH<sub>2</sub>-, 1-methyl-4-piperazinyl-CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, (2-methyl-1-imidazolyl)-CH<sub>2</sub>-, 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH<sub>2</sub>-, phthalimidylethylenyl, 1-azepanyl-CH<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-CH<sub>2</sub>-, 4-
- 15 (methyl)phenoxy-methylenyl, 4-(N,N-dimethylaminomethylenyl)phenoxy-methylenyl, methylaminothiocarbonyl, methoxymethylenyl, ethylaminothiocarbonyl, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminoethylenyl, N-methylaminomethylenyl, N-
- 20 (hydroxypropyl)aminomethylenyl, N-ethylaminomethylenyl, Boc-aminoethoxymethylenyl, aminoethoxymethylenyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, 2-pyrrolidinylmethoxy, 1-methyl-2-pyrrolidinylmethoxy, azetidin-3-ylmethoxy,
- 25 N-Boc-azetidin-3-ylmethoxy, N-Boc-piperidin-4-ylethoxy, 1-methyl-4-piperidinylethoxy, 4-piperidinylethoxy, 4-piperidinylmethoxy, N,N-dimethylaminoethoxy, 3-tetrahydrofuryl-0-, 3-tetrahydrofurylmethoxy, 4-tetrahydrofurylmethoxy, 4-methylphenoxy, 4-
- 30 (aminoethyl)phenoxy, 4-(1-imidazolyl)phenoxy, 2,4-dimethylphenoxy, phenoxy, 4-cyanophenoxy, 4-

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- [1,3]dioxolan-2-ylphenoxy, 4-fluorophenoxy, 3,4-difluorophenoxy, ethoxycarbonyl, morpholinylethylenylaminocarbonyl, morpholinylpropylenylaminocarbonyl, 1-
- 5 piperidinylcarbonyl, methylaminocarbonyl, ethylaminocarbonyl, N,N-diethylaminocarbonyl, N-(N',N'-dimethylaminoethylenyl)aminocarbonyl, aminocarbonyl, morpholinylethylenylamino, morpholinylpropylenylamino, N,N-diethylamino, N,N-dimethylamino, N,N-
- 10 diethylamino(2-propylenyl)aminomethylenyl, N,N-diethylamino(1-propylenyl)aminomethylenyl and N-(N',N'-dimethylaminoethylenyl)amino; and wherein R<sup>2</sup> is selected from
- phenyl substituted with a substituent
- 15 selected from amino, aminosulfonyl, cyano, N,N-dimethylamino, ethoxy, fluoro, hydroxyl, methoxy, nitro, methylcarbonylamino, 4-morpholinylsulfonyl, phenylsulfonylamino, (4-
- chlorophenyl)aminosulfonyl, trifluoromethyl,
- 20 trifluoromethoxy and -SO<sub>2</sub>NHC(O)CF<sub>3</sub>,
- pyrazinyl,
- pyrimidinyl,
- morpholinyl,
- piperidinyl,
- 25 piperazinyl optionally substituted with methyl, ethyl or propyl,
- pyridazinyl and
- pyridyl unsubstituted or substituted with one or more
- substituents independently selected from chloro,
- 30 fluoro, bromo, amino, methoxy, ethoxy, 1,1,1-trifluoroethoxy and trifluoromethylcarbonylamino.

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19. Compound of Claim 1 and pharmaceutically acceptable salts thereof selected from:

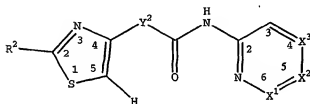
- 5 1-pyridin-2-yl-3-(2-pyridin-4-ylthiazol-4-yl)urea;  
1-(6-ethylpyridin-2-yl)-3-(2-pyridin-4-ylthiazol-4-yl)urea;  
1-(2-pyridin-4-yl-thiazol-4-yl)-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)urea;  
10 1-(6-(diethylaminomethyl)pyridin-2-yl)-3-(2-pyridin-4-ylthiazol-4-yl)urea;  
1-[6-(4-methylpiperazin-1-yl)pyridin-2-yl]-3-(2-pyridin-4-ylthiazol-4-yl)urea;  
1-[6-(piperidin-1-ylmethyl)pyridin-2-yl]-3-[2-(pyridin-4-yl)thiazol-4-yl]urea;  
15 1-(6-phenoxy-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea;  
1-[2-(2-ethoxy-pyridin-4-yl)-thiazol-4-yl]-3-(6-ethyl-pyridin-2-yl)-urea;  
20 1-(6-diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)-urea;  
1-[2-(2-methoxy-pyridin-4-yl)-thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)-urea;  
1-(2-pyridin-4-yl-thiazol-4-yl)-3-(6-pyrrolidin-1-ylmethyl-pyridin-2-yl)-urea;  
25 1-(2-phenylthiazol-4-yl)-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea;  
1-[6-(1-methylpyrrolidin-2-ylmethoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea;  
30 1-[2-(4-aminophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea; and

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1-(6-[4-(2-aminoethyl)phenoxy]pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea.

20. A compound of Claim 1 having Formula II

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II

wherein X<sup>1</sup> is CR<sup>1</sup> or N; wherein X<sup>2</sup> is CR<sup>1</sup> or N; wherein X<sup>3</sup> is CH or N; provided only one of X<sup>1</sup>, X<sup>2</sup> and X<sup>3</sup> can be N;

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wherein R<sup>1</sup> is one or more substituents selected from H, optionally substituted pyrrolidinyl, optionally substituted piperazinyl, optionally substituted piperidinyl, morpholinyl, 1,4-dioxo-8-aza-spiro[4.5]decyl, pyridyl, phenyl, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkyl, amino, C<sub>1</sub>-C<sub>4</sub>-azidoalkyl, C<sub>1</sub>-C<sub>4</sub>-cyanoalkyl, C<sub>1</sub>-C<sub>4</sub>-aminoalkyl, halo, hydroxy, (optionally substituted pyrrolidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperazinyl)-C<sub>1</sub>-C<sub>2</sub>-, morpholinyl-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted imidazolyl)-C<sub>1</sub>-C<sub>2</sub>-, phthalimidyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted azepanyl-C<sub>1</sub>-C<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted phenoxy-C<sub>1</sub>-C<sub>2</sub>-, C<sub>1</sub>-C<sub>4</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy,

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- optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy,  
optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy,  
optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-O-,  
5 tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted  
pyridyloxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-  
alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-  
alkylaminocarbonyl, 5-6-membered N-containing  
heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-  
10 C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl,  
aminocarbonyl, 5-6-membered N-containing  
heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-  
C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-C<sub>4</sub>-  
alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino;
- 15 wherein R<sup>2</sup> is selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-  
alkylamino-C<sub>2</sub>-C<sub>4</sub>-alkynyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl,  
optionally substituted benzodioxolyl, optionally  
substituted indolyl, optionally substituted  
phenoxy, unsubstituted 5-membered oxygen or sulfur  
20 containing heteroaryl, unsubstituted 6-membered  
nitrogen-containing heterocyclyl, phenyl optionally  
substituted with one or two substituents selected  
from halo, C<sub>1</sub>-C<sub>4</sub>-alkylamino, amino, nitro, C<sub>1</sub>-C<sub>4</sub>-  
alkoxy, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-  
25 alkylthio, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonylamino, (optionally  
substituted phenyl)sulfonylamino, cyano, C<sub>1</sub>-C<sub>2</sub>-  
haloalkoxy, 5- or 6-membered N-containing  
heterocyclyl, aminosulfonyl, (6-membered N-  
containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-  
30 haloalkylcarbonylaminosulfonyl and (optionally  
substituted phenyl)aminosulfonyl, and

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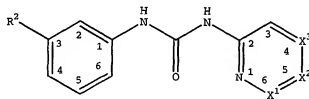
6-membered nitrogen-containing heterocyclyl  
substituted with one or more substituents  
independently selected from pyridyl, phenyl,

5 C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy,  
amino, halo, piperidinyl, morpholinyl, C<sub>1</sub>-C<sub>2</sub>  
alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub> alkylaminothiocarbonyl,  
N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, N-C<sub>1</sub>-C<sub>2</sub>-  
alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-  
alkylenylaminocarbonyl, aminocarbonyl, C<sub>1</sub>-C<sub>2</sub>-  
10 haloalkylcarbonylamino, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-  
alkylenylamino, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino and  
N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino;  
and

wherein Y<sup>2</sup> is selected from O, NH and CH<sub>2</sub>;

15 and pharmaceutically acceptable salts thereof.

21. A compound of Claim 1 having the formula



III

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wherein X<sup>1</sup> is CR<sup>1</sup> or N; wherein X<sup>2</sup> is CR<sup>1</sup> or N; wherein  
X<sup>3</sup> is CH or N; provided only one of X<sup>1</sup>, X<sup>2</sup> and X<sup>3</sup> can  
be N;

wherein R<sup>1</sup> is one or more substituents independently  
25 selected from H, optionally substituted  
pyrrolidinyl, optionally substituted piperazinyl,  
optionally substituted piperidinyl, morpholinyl,  
1,4-dioxo-8-aza-spiro[4.5]decyl, pyridyl, phenyl,

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C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkyl, amino, C<sub>1</sub>-C<sub>4</sub>-azidoalkyl, C<sub>1</sub>-C<sub>4</sub>-cyanoalkyl, C<sub>1</sub>-C<sub>4</sub>-aminoalkyl, halo, hydroxy, (optionally substituted pyrrolidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperazinyl)-C<sub>1</sub>-C<sub>2</sub>-, morpholinyl-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted imidazolyl)-C<sub>1</sub>-C<sub>2</sub>-, phthalimidyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted azepanyl-C<sub>1</sub>-C<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted phenoxy-C<sub>1</sub>-C<sub>2</sub>-, C<sub>1</sub>-C<sub>4</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-O-, tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted pyridyloxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, aminocarbonyl, 5-6-membered N-containing heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino; and

wherein R<sup>2</sup> is selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>2</sub>-C<sub>4</sub>-alkynyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted

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phenoxy, unsubstituted 5-membered oxygen or sulfur containing heteroaryl, unsubstituted 5- or 6-membered nitrogen-containing heterocyclyl, phenyl optionally substituted with one or two substituents selected

5 from halo, C<sub>1</sub>-C<sub>4</sub>-alkylamino, amino, nitro, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonylamino, (optionally substituted phenyl)sulfonylamino, cyano, C<sub>1</sub>-C<sub>2</sub>-haloalkoxy, 5- or 6-membered N-containing heterocyclyl, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylaminosulfonyl and (optionally substituted phenyl)aminosulfonyl, and

10 6-membered nitrogen-containing heterocyclyl substituted with one or more substituents independently selected from pyridyl, phenyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy, amino, halo, piperidiny, morpholinyl, C<sub>1</sub>-C<sub>2</sub>

20 alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub> alkylaminothiocarbonyl, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, N-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, aminocarbonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylamino, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-

25 alkylamino, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino and N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino; and pharmaceutically acceptable salts thereof.

22. Compound of Claim 21 wherein X<sup>1</sup> is CR<sup>1</sup>;  
30 wherein X<sup>2</sup> is CR<sup>1</sup>; wherein X<sup>3</sup> is CH; provided X<sup>2</sup> is CH when X<sup>1</sup> is not CH;

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wherein R<sup>1</sup> is independently selected from H, methyl, ethyl, propyl, 1-methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, 1-piperidinyl-CH<sub>2</sub>-, 4-methyl-1-piperidinyl-CH<sub>2</sub>-, 3-methyl-1-piperidinyl-CH<sub>2</sub>-, 2-methyl-1-piperidinyl-CH<sub>2</sub>-, 3,5-dimethyl-1-piperidinyl-CH<sub>2</sub>-, 4-oxo-1-piperidinyl-CH<sub>2</sub>-, 4-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 3-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 2-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-propylamino)-1-piperidinyl-CH<sub>2</sub>-, 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminomethylenyl, N-ethylaminomethylenyl and N,N-diethylamino; and

wherein R<sup>2</sup> is 3-(N,N-dimethylamino)-1-propynyl, 3-fluorophenyl, 4-fluorophenyl, 4-(N,N-dimethylamino)phenyl, 3-(methylcarbonylamino)phenyl, phenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminophenyl, 3-aminophenyl, 4-aminosulfonylphenyl, 4-(4-morpholinylsulfonyl)phenyl, 4-(trifluoroacetylaminosulfonyl)phenyl, 4-(trifluoromethylcarbonylamino sulfonyl)phenyl, 4-[(4-chlorophenyl)aminosulfonyl]phenyl, 3-(phenylsulfonylamino)phenyl, 2,4-difluorophenyl, 2,4-dimethoxyphenyl, 3-hydroxyphenyl, 4-

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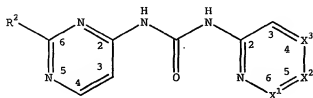
hydroxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl,  
4-methylthiophenyl, 4-cyanophenyl, 4-  
trifluoromethoxyphenyl, 4-methoxyphenyl, 3-  
nitrophenyl, 3-methoxyphenyl, 2-methoxyphenyl, 2-  
5 thiazolyl, 2-pyrazinyl, 5-pyrimidinyl, 4-methyl-1-  
piperazinyl, 4-morpholinyl, 6-methoxy-3-pyridyl, 2-  
methoxy-3-pyridyl, 2-ethoxy-3-pyridyl, 3,4-dichloro-  
4-pyridyl, 6-(trifluoromethylcarbonylamino)-3-  
pyridyl, 6-amino-3-pyridyl, 3,5-dichloro-4-pyridyl,  
10 2-chloro-4-pyridyl, 3-pyridyl and 4-pyridyl;  
and pharmaceutically acceptable salts thereof.

23. Compound of Claim 22 wherein  $R^1$  is selected  
from ethyl, propyl, 1-methyl-4-piperazinyl, 1-  
15 piperidinyl- $CH_2$ -, 4-morpholinyl- $CH_2$ -, N,N-  
diethylaminomethylenyl and N,N-diethylamino; and  
wherein  $R^2$  is 5-pyrimidinyl, 2-pyrazinyl, morpholinyl,  
4-methylpiperazinyl, 4-fluorophenyl, 4-(N,N-  
dimethylamino)propynyl, 3-nitrophenyl, 3-aminophenyl,  
20 4-aminosulfonylphenyl, 3-aminosulfonylphenyl, 3-  
(phenylsulfonylamino)phenyl, 3-  
(methylcarbonylamino)phenyl, 4-  
[(trifluoromethylcarbonyl)aminosulfonyl]phenyl, 4-  
hydroxyphenyl, 4-methoxyphenyl, 2-thiazolyl, 6-  
25 (trifluoromethylcarbonylamino)-3-pyridyl, 6-amino-3-  
pyridyl, 3-pyridyl and 4-pyridyl;  
and pharmaceutically acceptable salts thereof.

24. A compound of Claim 1 having the formula

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wherein  $X^1$  is  $CR^1$  or N; wherein  $X^2$  is  $CR^1$  or N; wherein  $X^3$  is CH or N; provided only one of  $X^1$ ,  $X^2$  and  $X^3$  can be N;

wherein  $R^1$  is one or more substituents independently selected from H, optionally substituted pyrrolidinyl, optionally substituted piperazinyl, optionally substituted piperidinyl, morpholinyl, 1,4-dioxo-8-aza-spiro[4.5]decyl, pyridyl, phenyl,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_2$ -haloalkyl,  $C_1$ - $C_4$ -hydroxyalkyl, amino,  $C_1$ - $C_4$ -azidoalkyl,  $C_1$ - $C_4$ -cyanoalkyl,  $C_1$ - $C_4$ -aminoalkyl, halo, hydroxy, (optionally substituted pyrrolidinyl)- $C_1$ - $C_2$ -, (optionally substituted piperidinyl)- $C_1$ - $C_2$ -, (optionally substituted piperazinyl)- $C_1$ - $C_2$ -, morpholinyl- $C_1$ - $C_2$ -, (optionally substituted imidazolyl)- $C_1$ - $C_2$ -, phthalimidyl- $C_1$ - $C_2$ -, optionally substituted azepanyl- $C_1$ - $C_2$ -, 1,4-dioxo-8-aza-spiro[4.5]decyl- $C_1$ - $C_2$ -, optionally substituted phenoxy- $C_1$ - $C_2$ -,  $C_1$ - $C_4$ -alkylaminothiocarbonyl,  $C_1$ - $C_4$ -alkoxy- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -hydroxyalkylamino- $C_1$ - $C_4$ -alkyl, amino- $C_1$ - $C_4$ -alkoxy- $C_1$ - $C_4$ -alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted pyrrolidinyl- $C_1$ - $C_4$ -alkoxy, optionally substituted azetidyl- $C_1$ - $C_4$ -alkoxy, optionally substituted piperidinyl- $C_1$ - $C_4$ -alkoxy,  $C_1$ - $C_4$ -alkylamino- $C_1$ - $C_4$ -alkoxy, tetrahydrofuryl-O-, tetrahydrofuryl- $C_1$ - $C_4$ -alkoxy, optionally substituted

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- pyridyloxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, aminocarbonyl, 5-6-membered N-containing heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino; and
- wherein R<sup>2</sup> is halo, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>2</sub>-C<sub>4</sub>-alkynyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, 5-membered oxygen or sulfur containing heteroaryl, 5- or 6-membered nitrogen-containing heterocyclyl, phenyl optionally substituted with one or two substituents selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkylamino, amino, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, cyano, C<sub>1</sub>-C<sub>2</sub>-haloalkyloxy, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylaminosulfonyl, and (optionally substituted phenyl)aminosulfonyl, and 6-membered nitrogen-containing heterocyclyl substituted with one or more substituents independently selected from pyridyl, phenyl, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, C<sub>1</sub>-C<sub>2</sub>-alkoxy, halo, piperidinyl, morpholinyl, C<sub>1</sub>-C<sub>2</sub>-alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub>-alkylaminothiocarbonyl, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, N-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, aminocarbonyl,

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morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino and N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino; and pharmaceutically acceptable salts thereof.

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25. Compound of Claim 24 wherein X<sup>1</sup> is CR<sup>1</sup>; wherein X<sup>2</sup> is CH; wherein X<sup>3</sup> is CH; provided X<sup>2</sup> is CH when X<sup>1</sup> is not CH; wherein R<sup>1</sup> is independently selected from methyl,

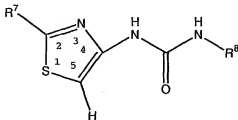
- 10 ethyl, propyl, 1-methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, 1-piperidinyl-CH<sub>2</sub>-, 4-methyl-1-piperidinyl-CH<sub>2</sub>-, 3-methyl-1-piperidinyl-CH<sub>2</sub>-, 2-methyl-1-piperidinyl-CH<sub>2</sub>-,
- 15 3,5-dimethyl-1-piperidinyl-CH<sub>2</sub>-, 4-oxo-1-piperidinyl-CH<sub>2</sub>-, 4-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 3-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 2-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-,
- 20 4-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-propylamino)-1-piperidinyl-CH<sub>2</sub>-, 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH<sub>2</sub>-, 4-
- 25 morpholinyl-CH<sub>2</sub>-, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminomethylenyl, N-ethylaminomethylenyl and N,N-diethylamino; and wherein R<sup>2</sup> is 3-fluorophenyl, 4-fluorophenyl, 4-(N,N-dimethylamino)phenyl, 3-(methylcarbonylamino)phenyl,
- 30 phenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminophenyl, 3-aminophenyl,

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4-aminosulfonylphenyl, 4-(4-morpholinylsulfonyl)phenyl, 4-(trifluoroacetylaminosulfonyl)phenyl, 4-(trifluoromethylcarbonylamino sulfonyl)phenyl, 4-[(4-chlorophenyl)aminosulfonyl]phenyl, 3-(phenylsulfonylamino)phenyl, 2,4-difluorophenyl, 2,4-dimethoxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 4-methylthiophenyl, 4-cyanophenyl, 4-trifluoromethoxyphenyl, 4-methoxyphenyl, 3-nitrophenyl, 3-methoxyphenyl, 2-methoxyphenyl, 2-thiazolyl, 2-pyrazinyl, 5-pyrimidinyl, 4-methyl-1-piperazinyl, 4-morpholinyl, 6-methoxy-3-pyridyl, 2-methoxy-3-pyridyl, 2-ethoxy-3-pyridyl, 3,4-dichloro-4-pyridyl, 6-(trifluoromethylcarbonylamino)-3-pyridyl, 6-amino-3-pyridyl, 3,5-dichloro-4-pyridyl, 2-chloro-4-pyridyl, 3-pyridyl and 4-pyridyl; and pharmaceutically acceptable salts thereof.

26. Compound of Claim 25 wherein  $R^1$  is selected from ethyl, propyl and 1-methyl-4-piperazinyl; and wherein  $R^2$  is 4-pyridyl; and pharmaceutically acceptable salts thereof.

27. A compound of Claim 1 having the formula



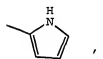
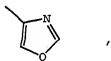
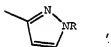
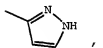
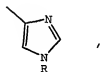
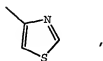
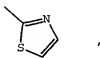
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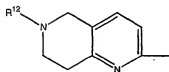
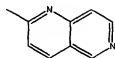
wherein R<sup>7</sup> is selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, 5-membered oxygen or sulfur containing heteroaryl, 6-membered nitrogen-containing heterocyclyl, phenyl optionally substituted with one or two substituents selected from halo, C<sub>1</sub>-C<sub>4</sub>-alkylamino, amino, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkylthio, cyano, C<sub>1</sub>-C<sub>2</sub>-haloalkyloxy, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C<sub>1</sub>-C<sub>2</sub>-haloalkylcarbonylamino-sulfonyl, and (optionally substituted phenyl)aminosulfonyl, and 6-membered nitrogen-containing heterocyclyl substituted with one or more substituents independently selected from pyridyl, phenyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy, halo, piperidinyl, morpholinyl, C<sub>1</sub>-C<sub>2</sub> alkylpiperazinyl, C<sub>1</sub>-C<sub>3</sub> alkylaminothiocarbonyl, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, N-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylaminocarbonyl, aminocarbonyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino, N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino and N,N-di-C<sub>1</sub>-C<sub>2</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylenylamino;

wherein R<sup>8</sup> is selected from

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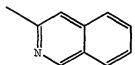
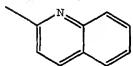
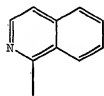
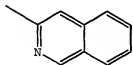
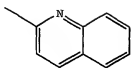


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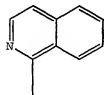


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and



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wherein R<sup>8</sup> is optionally substituted with one or two substituents independently selected from H, optionally substituted pyrrolidinyl, optionally substituted piperazinyl, optionally substituted piperidinyl, morpholinyl, 1,4-dioxo-8-aza-spiro[4.5]decyl, pyridyl, phenyl, C<sub>1</sub>-C<sub>6</sub>-alkyl,

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C<sub>1</sub>-C<sub>2</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkyl, amino, C<sub>1</sub>-C<sub>4</sub>-azidoalkyl, C<sub>1</sub>-C<sub>4</sub>-cyanoalkyl, C<sub>1</sub>-C<sub>4</sub>-aminoalkyl, halo, hydroxy, (optionally substituted pyrrolidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperidinyl)-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted piperazinyl)-C<sub>1</sub>-C<sub>2</sub>-, morpholinyl-C<sub>1</sub>-C<sub>2</sub>-, (optionally substituted imidazolyl)-C<sub>1</sub>-C<sub>2</sub>-, phthalimidyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted azepanyl-C<sub>1</sub>-C<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-C<sub>1</sub>-C<sub>2</sub>-, optionally substituted phenoxy-C<sub>1</sub>-C<sub>2</sub>-, C<sub>1</sub>-C<sub>4</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, (1-azabicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-O-, tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted pyridyloxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, 5-6-membered heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, aminocarbonyl, 5-6-membered N-containing heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino; and

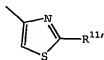
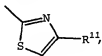
wherein R<sup>12</sup> is selected from H, and C<sub>1</sub>-C<sub>4</sub> alkyl.

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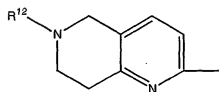
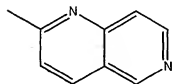
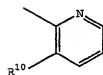
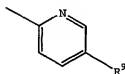
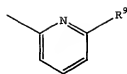
and pharmaceutically acceptable salts thereof.

28. Compound of Claim 27 wherein  $R^7$  is selected from halo,  $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_6$ -cycloalkyl, optionally substituted pyrimidinyl, morpholinyl, optionally substituted piperidinyl, optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, optionally substituted thienyl, phenyl optionally substituted with one or two substituents selected from halo,  $C_1$ - $C_4$ -alkylamino, Boc-amino, amino,  $C_1$ - $C_4$ -alkoxy,  $C_1$ - $C_2$ -haloalkyl, hydroxy,  $C_1$ - $C_4$ -alkylthio, cyano,  $C_1$ - $C_2$ -haloalkyloxy, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl,  $C_1$ - $C_2$ -haloalkylcarbonylaminosulfonyl, and (optionally substituted phenyl)aminosulfonyl, and pyridyl optionally substituted with one or two substituents selected from  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_4$ -alkoxy and halo;

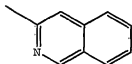
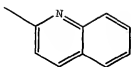
- 20 wherein  $R^8$  is selected from



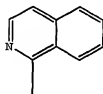
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and



wherein R<sup>9</sup> is selected from optionally substituted  
 pyrrolidinyl, optionally substituted  
 5 piperazinyl, optionally substituted  
 piperidinyl, morpholinyl, 1,4-dioxo-8-aza-  
 spiro[4.5]decyl, pyridyl, phenyl, C<sub>1</sub>-C<sub>4</sub> alkyl,  
 C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> hydroxyalkyl, amino, C<sub>1</sub>-C<sub>2</sub>  
 azidoalkyl, C<sub>1</sub>-C<sub>2</sub> cyanoalkyl, C<sub>1</sub>-C<sub>2</sub> aminoalkyl,  
 10 halo, (optionally substituted pyrrolidinyl)CH<sub>2</sub>-  
 , (optionally substituted piperidinyl)-CH<sub>2</sub>-,  
 (optionally substituted piperazinyl)-CH<sub>2</sub>-, 4-  
 morpholinyl-CH<sub>2</sub>-, (optionally substituted  
 imidazolyl)-CH<sub>2</sub>-, phthalimidylethyl, optionally  
 15 substituted azepanyl-CH<sub>2</sub>-, 1,4-dioxo-8-aza-  
 spiro[4.5]decyl-CH<sub>2</sub>-, optionally substituted  
 phenoxy-CH<sub>2</sub>-, C<sub>1</sub>-C<sub>4</sub>-alkylaminothiocarbonyl, C<sub>1</sub>-  
 C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-  
 alkyl, C<sub>1</sub>-C<sub>4</sub>-hydroxyalkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, Boc-

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- aminoethoxymethylenyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted pyrrolidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted azetidiny-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted piperidinyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, tetrahydrofuryl-O-, tetrahydrofuryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally substituted phenoxy, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, 1-piperidinylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl, aminocarbonyl, morpholinyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, and C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkylamino;
- wherein R<sup>10</sup> is selected from H, hydroxy, and amino;
- wherein R<sup>11</sup> is selected from pyridyl and pyrimidinyl; and
- wherein R<sup>12</sup> is selected from H, and C<sub>1</sub>-C<sub>4</sub> alkyl, and pharmaceutically acceptable salts thereof.

29. Compound of Claim 28 wherein R<sup>7</sup> is selected from bromo, chloro, fluoro, C<sub>1</sub>-C<sub>3</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, optionally substituted pyrimidinyl, morpholinyl, piperidinyl, benzodioxolyl, indolyl, phenoxy, thienyl, phenyl optionally substituted with one or two substituents selected from fluoro, N,N-dimethylamino, amino, methoxy, trifluoromethyl, Boc-amino, hydroxy, ethoxy, methylthio, cyano, trifluoromethoxy, aminosulfonyl, 4-morpholinylsulfonyl,

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trifluoroacetylaminosulfonyl, and (4-chlorophenyl)aminosulfonyl,

and pyridyl optionally substituted with one or two substituents selected from C<sub>1</sub>-C<sub>3</sub> alkyl, methoxy, ethoxy

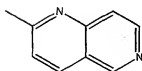
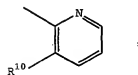
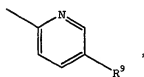
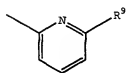
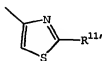
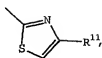
5 and chloro;

and pharmaceutically acceptable salts thereof.

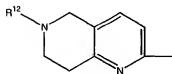
30. Compound of Claim 29 wherein R<sup>7</sup> is selected from bromo, methyl, ethyl, cyclopropyl, cyclohexyl, 3-fluorophenyl, 4-fluorophenyl, 4-(N,N-dimethylamino)phenyl, phenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminophenyl, 3-aminophenyl, 4-Boc-aminophenyl, 4-aminosulfonylphenyl, 4-(4-morpholinylsulfonyl)phenyl, 4-(trifluoroacetylaminosulfonyl)phenyl, 4-[(4-chlorophenyl)aminosulfonyl]phenyl, 2,4-difluorophenyl, 5-benzodioxolyl, 2,4-dimethoxyphenyl, 3-hydroxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 4-methylthiophenyl, 5-indolyl, 4-cyanophenyl, 4-trifluoromethoxyphenyl, 4-methoxyphenyl, 3-methoxyphenyl, 2-methoxyphenyl, phenoxy, 2-thienyl, 4-pyrimidinyl, 2-methylthio-4-pyrimidinyl, morpholinyl, 4-piperidinyl, 6-methoxy-3-pyridyl, 2-methoxy-3-pyridyl, 2-ethoxy-3-pyridyl, 3,4-dichloro-4-pyridyl, 3,5-dichloro-4-pyridyl, 2-chloro-4-pyridyl, 3-pyridyl and 4-pyridyl;

wherein R<sup>8</sup> is selected from

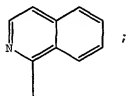
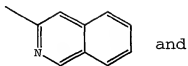
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wherein R<sup>9</sup> is selected from 3-(N,N-dimethylamino)-  
 1-pyrrolidinyl, 1-methyl-4-piperazinyl, 1-benzyl-4-  
 5 piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-  
 pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, 4-amino-  
 1-piperidinyl, 4-(N-hydroxyethylamino)-1-piperidinyl,  
 4-(N-propylamino)-1-piperidinyl, 4-(N-benzylamino)-1-  
 piperidinyl, 4-oxo-piperidinyl, 4-(hydroxyimino)-  
 10 piperidinyl, 4-morpholinyl, 1,4-dioxo-8-aza-  
 spiro[4.5]decyl, pyridyl, phenyl, methyl, ethyl,  
 propyl, amino, azidomethyl, hydroxymethyl,  
 trifluoromethyl, fluoro, chloro, bromo, aminoethyl,  
 aminomethyl, cyanomethyl, 1-pyrrolidinyl-CH<sub>2</sub>-, 2-  
 15 methoxycarbonyl-1-pyrrolidinyl-CH<sub>2</sub>-, 2-carboxy-1-  
 pyrrolidinyl-CH<sub>2</sub>-, 2-hydroxymethyl-1-pyrrolidinyl-CH<sub>2</sub>-,  
 1-piperidinyl-CH<sub>2</sub>-, 4-methyl-1-piperidinyl-CH<sub>2</sub>-, 3-  
 methyl-1-piperidinyl-CH<sub>2</sub>-, 2-methyl-1-piperidinyl-CH<sub>2</sub>-,  
 3,5-dimethyl-1-piperidinyl-CH<sub>2</sub>-, 4-oxo-1-piperidinyl-  
 20 CH<sub>2</sub>-, 4-hydroxy-1-piperidinyl-CH<sub>2</sub>-, 3-hydroxy-1-  
 piperidinyl-CH<sub>2</sub>-, 2-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-,  
 3-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-, 3-carboxy-1-  
 piperidinyl-CH<sub>2</sub>-, 4-ethoxycarbonyl-1-piperidinyl-CH<sub>2</sub>-,

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- 4-carboxy-1-piperidinyl-CH<sub>2</sub>-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH<sub>2</sub>-, 4-(N-propylamino)-1-piperidinyl-CH<sub>2</sub>-, 1-methyl-4-piperazinyl-CH<sub>2</sub>-, 4-morpholinyl-CH<sub>2</sub>-, (2-
- 5 methyl-1-imidazolyl-CH<sub>2</sub>-, 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH<sub>2</sub>-, phthalimidylethylenyl, 1-azepanyl-CH<sub>2</sub>-, 1,4-dioxo-8-aza-spiro[4.5]decyl-CH<sub>2</sub>-, 4-(methyl)phenoxy-methylenyl, 4-(N,N-dimethylaminomethylenyl)phenoxy-methylenyl,
- 10 methylaminothiocarbonyl, methoxymethylenyl, ethylaminothiocarbonyl, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminomethylenyl, N-(hydroxypropyl)aminomethylenyl, N-ethylaminomethylenyl, Boc-aminoethoxymethylenyl, aminoethoxymethylenyl, (1-
- 15 aza-bicyclo[2.2.2]oct-3-yl)-oxy, 2-pyrrolidinylmethoxy, 1-methyl-2-pyrrolidinylmethoxy, azetidin-3-ylmethoxy, N-Boc-azetidin-3-ylmethoxy, N-Boc-piperidin-4-ylethoxy, 1-methyl-4-piperidinylethoxy, 4-piperidinylethoxy, 4-piperidinylmethoxy, N,N-dimethylaminoethoxy, 3-
- 20 tetrahydrofuryl-O-, 3-tetrahydrofurylmethoxy, 4-tetrahydrofurylmethoxy, 4-methylphenoxy, 4-(aminoethyl)phenoxy, 4-(1-imidazolyl)phenoxy, 2,4-dimethylphenoxy, phenoxy, 4-cyanophenoxy, 4-[1,3]dioxolan-2-ylphenoxy, 4-fluorophenoxy, 3,4-
- 25 difluorophenoxy, ethoxycarbonyl, morpholinylpropylenylaminocarbonyl, 1-piperidinylcarbonyl, methylaminocarbonyl, ethylaminocarbonyl, N,N-diethylaminocarbonyl, N-(N',N'-dimethylaminoethylenyl)aminocarbonyl, aminocarbonyl,
- 30 morpholinylpropylenylamino, N,N-diethylamino, N,N-diethylamino(2-propylenyl)aminomethylenyl, N,N-

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diethylamino(1-propylenyl)aminomethylenyl and N-(N',N'-dimethylaminoethylenyl)amino;

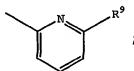
wherein R<sup>10</sup> is selected from H, hydroxy, and amino;

5 wherein R<sup>11</sup> is pyridyl; and

wherein R<sup>12</sup> is selected from H, methyl, ethyl and propyl;

and pharmaceutically acceptable salts thereof.

10 31. Compound of Claim 30 wherein R<sup>8</sup> is



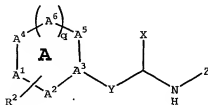
and pharmaceutically acceptable salts thereof.

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32. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Claim 1.

20

33. A method of inhibiting cell proliferation which comprises administering an effective amount of a compound of Formula I



I

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wherein each of A<sup>1</sup>-A<sup>6</sup> is selected from CH<sub>2</sub>, CH, C, O, S, NH and N; wherein A<sup>1</sup>-A<sup>6</sup> together form a ring A selected from

- 5            additionally substituted or unsubstituted 5- or 6-membered heterocyclyl,  
            additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group,  
            additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, and  
10          additionally substituted or unsubstituted phenyl, wherein the ring A is additionally substituted with one or more substituents independently selected from halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>,  
15          cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted phenyl, lower alkyl, cyano, lower hydroxyalkyl,  
20          nitro, lower alkenyl, lower alkynyl and lower haloalkyl;

wherein X and Z taken together form a nitrogen containing ring selected from

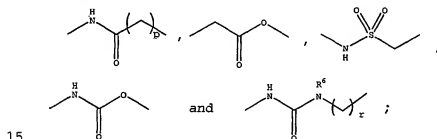
- unsubstituted 5-6 membered heterocyclyl,  
25          unsubstituted 5-6 membered heterocyclyl fused with a phenyl group,  
            5-6 membered heterocyclyl substituted with one or more substituents independently selected from R<sup>1</sup>, and

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5-6 membered nitrogen-containing heterocyclyl, fused with a phenyl group, substituted with one or more substituents independently selected from  $R^1$ ;

- wherein  $R^1$  is independently selected from H, halo, -  
 5  $OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-CONR^3R^3$ ,  $-NR^3R^3$ ,  
 $-C(S)NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-NR^3C(O)R^3$ ,  
 cycloalkyl, optionally substituted phenylalkylenyl,  
 optionally substituted 4-10 membered heterocyclyl,  
 optionally substituted 4-10 membered  
 10 heterocyclylalkyl, optionally substituted phenyl,  
 optionally substituted phenoxy, lower alkyl, lower  
 cyano, lower alkenyl, lower alkynyl and lower  
 haloalkyl;

wherein Y is selected from, in either orientation,



wherein  $R^2$  is selected from

- lower alkylaminoalkynyl,  
 substituted or unsubstituted phenyl,  
 20 substituted or unsubstituted 5-6 membered  
 heterocyclyl, and  
 substituted or unsubstituted 5-6 membered  
 heterocyclyl bridged with a phenyl group;  
 wherein substituted  $R^2$  is substituted with one or  
 25 more substituents independently selected from  
 halo,  $-OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  
 $-NR^3R^3$ ,  $-C(O)NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ , -

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NHC(O)R<sup>3</sup>, -SO<sub>2</sub>NHC(O)R<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, nitro,  
cycloalkyl, optionally substituted  
phenylalkylenyl, optionally substituted 4-7  
membered heterocyclyl, optionally substituted  
5 heterocyclylalkylenyl, optionally substituted  
phenyl, optionally substituted  
phenoxyalkylenyl, optionally substituted  
heterocyclyloxyalkyl, lower alkyl, cyano, lower  
hydroxyalkyl, lower alkoxyalkyl, lower  
10 azidoalkyl, lower aminoalkyl, lower  
(hydroxyalkyl)aminoalkyl, lower  
alkylaminoalkyl, lower alkylaminoalkoxy, lower  
aminoalkoxyalkyl, lower (alkylaminoalkyl)amino  
lower ((alkylamino)alkylamino)alkyl, lower  
15 alkylaminoalkylaminocarbonyl, lower cyanoalkyl,  
lower alkenyl, lower alkynyl and lower  
haloalkyl;

wherein R<sup>3</sup> is selected from H, lower alkyl, optionally  
substituted phenyl, optionally substituted  
20 phenylalkyl, optionally substituted heterocyclyl,  
optionally substituted heterocyclylalkyl, C<sub>3</sub>-C<sub>6</sub>  
cycloalkyl, and lower haloalkyl;

wherein R<sup>6</sup> is selected from H, alkyl, 5-6 membered  
heterocyclylalkylenyl and alkylamino;

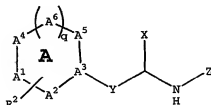
25 wherein p is 1 or 2;  
wherein q is 0 or 1; and  
wherein r is 0-3;

and pharmaceutically acceptable salts thereof;  
provided A is not thiazol-2-yl when Y is ureido.

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34. A method of treating cancer which comprises administering an effective amount of a compound of Formula I



5

I

wherein each of A<sup>1</sup>-A<sup>6</sup> is selected from CH<sub>2</sub>, CH, C, O, S, NH and N; wherein A<sup>1</sup>-A<sup>6</sup> together form a ring A selected from

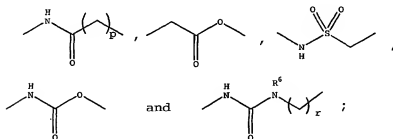
- 10      additionally substituted or unsubstituted 5- or 6-membered heterocyclyl,  
          additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group,  
          additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, and  
 15      additionally substituted or unsubstituted phenyl, wherein the ring A is additionally substituted with one or more substituents independently selected from halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>,  
 20      -COR<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>, cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted  
 25      phenyl, lower alkyl, cyano, lower hydroxyalkyl, nitro, lower alkenyl, lower alkynyl and lower haloalkyl;

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wherein X and Z taken together form a nitrogen  
 containing ring selected from  
 unsubstituted 5-6 membered heterocyclyl,  
 unsubstituted 5-6 membered heterocyclyl fused with a  
 5 phenyl group,  
 5-6 membered heterocyclyl substituted with one or  
 more substituents independently selected from R<sup>1</sup>,  
 and  
 5-6 membered nitrogen-containing heterocyclyl, fused  
 10 with a phenyl group, substituted with one or more  
 substituents independently selected from R<sup>1</sup>;

wherein R<sup>1</sup> is independently selected from H, halo, -  
 OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -CONR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>,  
 -C(S)NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>,  
 15 cycloalkyl, optionally substituted phenylalkenyl,  
 optionally substituted 4-10 membered heterocyclyl,  
 optionally substituted 4-10 membered  
 heterocyclylalkyl, optionally substituted phenyl,  
 optionally substituted phenoxy, lower alkyl, lower  
 20 cyano, lower alkenyl, lower alkynyl and lower  
 haloalkyl;

wherein Y is selected from, in either orientation,



25 wherein R<sup>2</sup> is selected from  
 lower alkylaminoalkynyl,  
 substituted or unsubstituted phenyl,

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substituted or unsubstituted 5-6 membered  
heterocyclyl, and

substituted or unsubstituted 5-6 membered  
heterocyclyl bridged with a phenyl group;

- 5        wherein substituted  $R^2$  is substituted with one or  
more substituents independently selected from  
halo,  $-OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-$   
 $NR^3R^3$ ,  $-C(O)NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-$   
10         $NHC(O)R^3$ ,  $-SO_2NHC(O)R^3$ ,  $-C(S)NR^3R^3$ , nitro,  
cycloalkyl, optionally substituted  
phenylalkylenyl, optionally substituted 4-7  
membered heterocyclyl, optionally substituted  
heterocyclylalkylenyl, optionally substituted  
phenyl, optionally substituted  
15        phenoxyalkylenyl, optionally substituted  
heterocyclcyloxyalkyl, lower alkyl, cyano, lower  
hydroxyalkyl, lower alkoxyalkyl, lower  
azidoalkyl, lower aminoalkyl, lower  
(hydroxyalkyl)aminoalkyl, lower  
20        alkylaminoalkyl, lower alkylaminoalkoxy, lower  
aminoalkoxyalkyl, lower (alkylaminoalkyl)amino  
lower ((alkylamino)alkylamino)alkyl, lower  
alkylaminoalkylaminocarbonyl, lower cyanoalkyl,  
lower alkenyl, lower alkynyl and lower  
25        haloalkyl;

- wherein  $R^3$  is selected from H, lower alkyl, optionally  
substituted phenyl, optionally substituted  
phenylalkyl, optionally substituted heterocyclyl,  
optionally substituted heterocyclylalkyl,  $C_3-C_6$   
30        cycloalkyl, and lower haloalkyl;

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wherein  $R^6$  is selected from H, alkyl, 5-6 membered heterocyclylalkylenyl and alkylamino;

wherein p is 1 or 2;

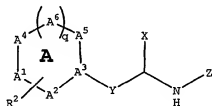
wherein q is 0 or 1; and

5 wherein r is 0-3;

and pharmaceutically acceptable salts thereof;

provided A is not thiazol-2-yl when Y is ureido.

35. A method of inhibiting a tyrosine kinase  
10 which comprises administering an effective amount of a compound of Formula I



I

- 15 wherein each of  $A^1$ - $A^6$  is selected from  $CH_2$ , CH, C, O, S, NH and N; wherein  $A^1$ - $A^6$  together form a ring A selected from

additionally substituted or unsubstituted 5- or 6-membered heterocyclyl,

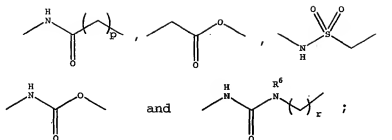
- 20 additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group, additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, and

- 25 additionally substituted or unsubstituted phenyl, wherein the ring A is additionally substituted with one or more substituents independently selected from halo,  $-OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-NR^3C(O)R^3$ ,

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- cycloalkyl, optionally substituted  
phenylalkylenyl, optionally substituted 5-6  
membered heterocyclyl, optionally substituted  
heteroarylalkylenyl, optionally substituted  
5 phenyl, lower alkyl, cyano, lower hydroxyalkyl,  
nitro, lower alkenyl, lower alkynyl and lower  
haloalkyl;  
wherein X and Z taken together form a nitrogen  
containing ring selected from  
10 unsubstituted 5-6 membered heterocyclyl,  
unsubstituted 5-6 membered heterocyclyl fused with a  
phenyl group,  
5-6 membered heterocyclyl substituted with one or  
more substituents independently selected from R<sup>1</sup>,  
15 and  
5-6 membered nitrogen-containing heterocyclyl, fused  
with a phenyl group, substituted with one or more  
substituents independently selected from R<sup>1</sup>;  
wherein R<sup>1</sup> is independently selected from H, halo, -  
20 OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -CONR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>,  
-C(S)NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>,  
cycloalkyl, optionally substituted phenylalkylenyl,  
optionally substituted 4-10 membered heterocyclyl,  
optionally substituted 4-10 membered  
25 heterocyclylalkyl, optionally substituted phenyl,  
optionally substituted phenoxy, lower alkyl, lower  
cyano, lower alkenyl, lower alkynyl and lower  
haloalkyl;  
wherein Y is selected from, in either orientation,

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wherein  $\text{R}^2$  is selected from

lower alkylaminoalkynyl,

5 substituted or unsubstituted phenyl,

substituted or unsubstituted 5-6 membered

heterocyclyl, and

substituted or unsubstituted 5-6 membered

heterocyclyl bridged with a phenyl group;

10 wherein substituted  $\text{R}^2$  is substituted with one or

more substituents independently selected from

halo,  $-\text{OR}^3$ ,  $-\text{SR}^3$ ,  $-\text{CO}_2\text{R}^3$ ,  $-\text{CO}_2\text{NR}^3\text{R}^3$ ,  $-\text{COR}^3$ , -

$\text{NR}^3\text{R}^3$ ,  $-\text{C}(\text{O})\text{NR}^3\text{R}^3$ ,  $-\text{SO}_2\text{NR}^3\text{R}^3$ ,  $-\text{NR}^3\text{C}(\text{O})\text{OR}^3$ , -

15  $\text{NHC}(\text{O})\text{R}^3$ ,  $-\text{SO}_2\text{NHC}(\text{O})\text{R}^3$ ,  $-\text{C}(\text{S})\text{NR}^3\text{R}^3$ , nitro,

cycloalkyl, optionally substituted

phenylalkylenyl, optionally substituted 4-7

membered heterocyclyl, optionally substituted

heterocyclylalkylenyl, optionally substituted

phenyl, optionally substituted

20 phenoxyalkylenyl, optionally substituted

heterocyclyloxyalkyl, lower alkyl, cyano, lower

hydroxyalkyl, lower alkoxyalkyl, lower

azidoalkyl, lower aminoalkyl, lower

(hydroxyalkyl)aminoalkyl, lower

25 alkylaminoalkyl, lower alkylaminoalkoxy, lower

aminoalkoxyalkyl, lower (alkylaminoalkyl)amino

lower ((alkylamino)alkylamino)alkyl, lower

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alkylaminoalkylaminocarbonyl, lower cyanoalkyl,  
lower alkenyl, lower alkynyl and lower  
haloalkyl;

wherein  $R^3$  is selected from H, lower alkyl, optionally  
substituted phenyl, optionally substituted  
phenylalkyl, optionally substituted heterocyclyl,  
optionally substituted heterocyclalkyl,  $C_3-C_6$   
cycloalkyl, and lower haloalkyl;

wherein  $R^6$  is selected from H, alkyl, 5-6 membered  
heterocyclalkylenyl and alkylamino;

wherein p is 1 or 2;

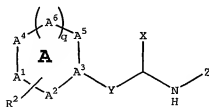
wherein q is 0 or 1; and

wherein r is 0-3;

and pharmaceutically acceptable salts thereof;

provided A is not thiazol-2-yl when Y is ureido.

36. A method of treating a neurological disorder  
which comprises administering an effective amount of a  
compound of Formula 1



I

wherein each of  $A^1-A^6$  is selected from  $CH_2$ , CH, C, O, S,  
NH and N; wherein  $A^1-A^6$  together form a ring A

selected from

additionally substituted or unsubstituted 5- or 6-  
membered heterocyclyl,

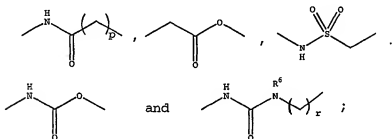
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- additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group, additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, and
- 5 additionally substituted or unsubstituted phenyl, wherein the ring A is additionally substituted with one or more substituents independently selected from halo,  $-OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-NR^3C(O)R^3$ ,
- 10 cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted phenyl, lower alkyl, cyano, lower hydroxyalkyl,
- 15 nitro, lower alkenyl, lower alkynyl and lower haloalkyl;
- wherein X and Z taken together form a nitrogen containing ring selected from
- unsubstituted 5-6 membered heterocyclyl,
- 20 unsubstituted 5-6 membered heterocyclyl fused with a phenyl group,
- 5-6 membered heterocyclyl substituted with one or more substituents independently selected from  $R^1$ , and
- 25 5-6 membered nitrogen-containing heterocyclyl, fused with a phenyl group, substituted with one or more substituents independently selected from  $R^1$ ;
- wherein  $R^1$  is independently selected from H, halo, - $OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-CONR^3R^3$ ,  $-NR^3R^3$ ,
- 30  $-C(S)NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-NR^3C(O)R^3$ , cycloalkyl, optionally substituted phenylalkylenyl,

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optionally substituted 4-10 membered heterocyclyl,  
 optionally substituted 4-10 membered  
 heterocyclylalkyl, optionally substituted phenyl,  
 optionally substituted phenoxy, lower alkyl, lower  
 5 cyano, lower alkenyl, lower alkynyl and lower  
 haloalkyl;

wherein Y is selected from, in either orientation,



10 wherein  $R^2$  is selected from  
 lower alkylaminoalkynyl,  
 substituted or unsubstituted phenyl,  
 substituted or unsubstituted 5-6 membered  
 heterocyclyl, and  
 15 substituted or unsubstituted 5-6 membered  
 heterocyclyl bridged with a phenyl group;  
 wherein substituted  $R^2$  is substituted with one or  
 more substituents independently selected from  
 halo,  $-OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ , -  
 20  $NR^3R^3$ ,  $-C(O)NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ , -  
 $NHC(O)R^3$ ,  $-SO_2NHC(O)R^3$ ,  $-C(S)NR^3R^3$ , nitro,  
 cycloalkyl, optionally substituted  
 phenylalkylenyl, optionally substituted 4-7  
 membered heterocyclyl, optionally substituted  
 25 heterocyclylalkylenyl, optionally substituted  
 phenyl, optionally substituted  
 phenoxyalkylenyl, optionally substituted

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- heterocyclyloxyalkyl, lower alkyl, cyano, lower hydroxyalkyl, lower alkoxyalkyl, lower azidoalkyl, lower aminoalkyl, lower (hydroxyalkyl)aminoalkyl, lower
- 5 alkylaminoalkyl, lower alkylaminoalkoxy, lower aminoalkoxyalkyl, lower (alkylaminoalkyl)amino lower ((alkylamino)alkylamino)alkyl, lower alkylaminoalkylaminocarbonyl, lower cyanoalkyl, lower alkenyl, lower alkynyl and lower
- 10 haloalkyl;
- wherein  $R^3$  is selected from H, lower alkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl,  $C_3-C_6$
- 15 cycloalkyl, and lower haloalkyl;
- wherein  $R^6$  is selected from H, alkyl, 5-6 membered heterocyclylalkylenyl and alkylamino;
- wherein p is 1 or 2;
- wherein q is 0 or 1; and
- 20 wherein r is 0-3;
- and pharmaceutically acceptable salts thereof;
- provided A is not thiazol-2-yl when Y is ureido.

37. Use of a compound of any of Claims 1-31 for

25 preparing a medicament for the treatment of cancer.

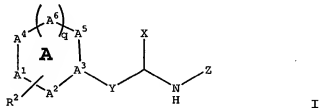
38. Use of a compound of any of Claims 1-31 for preparing a medicament for the treatment of a neurological disorder.

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39. Use of a compound of any of Claims 1-31 for preparing a medicament for the treatment of cell proliferation.

5 40. A compound of formula I



wherein each of A<sup>1</sup>-A<sup>6</sup> is selected from CH<sub>2</sub>, CH, C, O, S, NH and N; wherein A<sup>1</sup>-A<sup>6</sup> together form a ring A

10 selected from

additionally substituted or unsubstituted 5- or 6-membered heterocyclyl,

additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group,

15 additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, and

additionally substituted or unsubstituted phenyl, wherein the ring A is additionally substituted with one or more substituents independently

20 selected from halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>, cycloalkyl, optionally substituted

phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted

25 heteroarylalkylenyl, optionally substituted phenyl, lower alkyl, cyano, lower hydroxyalkyl, nitro, lower alkenyl, lower alkynyl and lower haloalkyl;

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wherein X and Z taken together form a nitrogen containing ring selected from unsubstituted 5-6 membered heterocyclyl, unsubstituted 5-6 membered heterocyclyl fused with a phenyl group,

5 5-6 membered heterocyclyl substituted with one or more substituents independently selected from  $R^1$ , and

5-6 membered nitrogen-containing heterocyclyl, fused

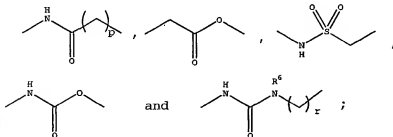
10 with a phenyl group, substituted with one or more substituents independently selected from  $R^1$ ;

wherein  $R^1$  is independently selected from H, halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -CONR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>,

15 cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted 4-10 membered heterocyclylalkyl, optionally substituted phenyl, optionally substituted phenoxy, lower alkyl, lower

20 cyano, lower alkenyl, lower alkynyl and lower haloalkyl;

wherein Y is selected from, in either orientation,



25 wherein  $R^2$  is selected from lower alkylaminoalkynyl, substituted or unsubstituted phenyl,

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substituted or unsubstituted 5-6 membered  
heterocyclyl, and

substituted or unsubstituted 5-6 membered  
heterocyclyl bridged with a phenyl group;

- 5        wherein substituted  $R^2$  is substituted with one or  
more substituents independently selected from  
halo,  $-OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $-$   
 $NR^3R^3$ ,  $-C(O)NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-$   
10         $NHC(O)R^3$ ,  $-SO_2NHC(O)R^3$ ,  $-C(S)NR^3R^3$ , nitro,  
cycloalkyl, optionally substituted  
phenylalkylenyl, optionally substituted 4-7  
membered heterocyclyl, optionally substituted  
heterocyclylalkylenyl, optionally substituted  
phenyl, optionally substituted  
15        phenoxyalkylenyl, optionally substituted  
heterocyclyloxyalkyl, lower alkyl, cyano, lower  
hydroxyalkyl, lower alkoxyalkyl, lower  
azidoalkyl, lower aminoalkyl, lower  
(hydroxyalkyl)aminoalkyl, lower  
20        alkylaminoalkyl, lower alkylaminoalkoxy, lower  
aminoalkoxyalkyl, lower (alkylaminoalkyl)amino  
lower ((alkylamino)alkylamino)alkyl, lower  
alkylaminoalkylaminocarbonyl, lower cyanoalkyl,  
lower alkenyl, lower alkynyl and lower  
25        haloalkyl;

- wherein  $R^3$  is selected from H, lower alkyl, optionally  
substituted phenyl, optionally substituted  
phenylalkyl, optionally substituted heterocyclyl,  
optionally substituted heterocyclylalkyl,  $C_3-C_6$   
30        cycloalkyl, and lower haloalkyl;

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wherein  $R^6$  is selected from H, alkyl, 5-6 membered

heterocyclalkylenyl and alkylamino;

wherein p is 1 or 2;

wherein q is 0 or 1; and

5 wherein r is 0-3;

and pharmaceutically acceptable salts thereof;

for use as an active therapeutic substance.

41. Compound of Claim 40 for its anti-neoplasia  
10 use.

42. Compound of Claim 40 for its use in the  
treatment of stroke.

15

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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IT,  
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(54) Title: UREA COMPOUNDS AND METHODS OF USES

(57) Abstract: Selected novel urea compounds are effective for prophylaxis and treatment of diseases, such as cell proliferation or apoptosis mediated diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving stroke, cancer and the like. The subject invention also relates to processes for making such compounds as well as to inter-mediate useful in such processes.

## INTERNATIONAL SEARCH REPORT

 International Application No.  
 PCT/US 01/25472

## A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 26203 A (ISACCHI ANTONELLA ;TRAQUANDI GABRIELLA (IT); VILLA MANUELA (IT); V) 11 May 2000 (2000-05-11) cited in the application claim 13; example 75 ---	19,20
Y	WO 99 24416 A (SQUIBB BRISTOL MYERS CO) 20 May 1999 (1999-05-20) cited in the application examples 351,483,569 ---	19,20
Y	WO 99 32106 A (BAYER AG) 1 July 1999 (1999-07-01) cited in the application claims 31,37,55; example 333 -----	19,20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered (novel) or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

17 January 2002

Date of mailing of the international search report

22.04.02

Name and mailing address of the ISA

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Authorized officer

Grassi, D

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/25472**Box I** Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-18  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

19, 20

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-18

Besides the problem with Rule 13(1) PCT the present claims 1-18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Moreover, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims 1-18 is impossible.

The claims 27-31 do not entirely fall within claim 1 and are therefore not clear (Article 6 PCT). The residue R8 in formula V of claim 27 appears to correspond to residue A in claim 1. However, R8 is (optionally) substituted with residues not falling within the definition of R2 in claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 19,20

Compounds in which A is thiazol-4-yl and Xz form a 6-membered ring as present in the examples 2, 4-14, 20, 25-36, etc.).

2. Claims: 21-23

Compounds in which A is substituted phenyl and XZ forms a 6-membered ring as in the examples 15, 54, or 234-289.

3. Claims: 24-26

Compounds in which A is pyrimidine and and YZ form a 6-membered Ring as in the examples 311-323.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 01/25472

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